PYRAZOLO'3,4-B! PYRIDINE COMPOUNDS, AND THEIR USE AS PHOSPHODIESTERASE INHIBITORS

The present invention relates to pyrazolo[3,4-b]pyridine compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the pyrazolo[3,4-b]pyridine compounds in therapy, for example as inhibitors of phosphodiesterase type IV (PDE4) and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis, allergic rhinitis or atopic dermatitis.

Background to the Invention

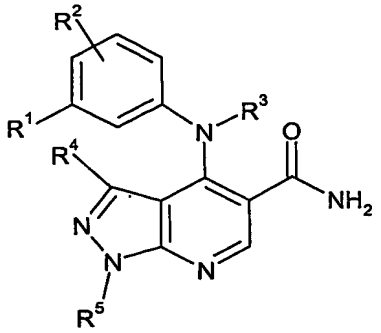
US 3,979,399, US 3,840,546, and US 3,966,746 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxamides wherein the 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 3-6-membered heterocyclic group such as pyrrolidino, piperidino and piperazino. The compounds are disclosed as central nervous system depressants useful as ataractic, analgesic and hypotensive agents.

US 3,925,388, US 3,856,799, US 3,833,594 and US 3,755,340 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxylic acids and esters. The 4-amino group NR_3R_4 can be an acyclic amino group wherein R_3 and R_4 may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR_3R_4 can alternatively be a 5-6-membered heterocyclic group in which an additional nitrogen is present such as pyrrolidino, piperidino, pyrazolyl, pyrimidinyl, pyridazinyl or piperazinyl. The compounds are mentioned as being central nervous system depressants useful as ataractic agents or tranquilisers, as having antiinflammatory and analgesic properties. The compounds are mentioned as increasing the intracellular concentration of adenosine-3',5'-cyclic monophosphate and for alleviating the symptoms of asthma.

H. Hoehn et al., *J. Heterocycl. Chem.*, 1972, 9(2), 235-253 discloses a series of 1*H*-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives with 4-hydroxy, 4-chloro, 4-alkoxy, 4-hydrazino, and 4-amino substituents.

CA 1003419, CH 553 799 and T.Denzel, *Archiv der Pharmazie*, 1974, 307(3), 177-186 disclose 4,5-disubstituted 1*H*-pyrazolo[3,4-b]pyridines unsubstituted at the 1-position.

Japanese laid-open patent application JP-2002-20386-A (Ono Yakuhin Kogyo KK) published on 23 January 2002 discloses pyrazolopyridine compounds of the following formula:



JP-2002-20386-A
(Ono)

wherein R^1 denotes 1) a group $-OR^6$, 2) a group $-SR^7$, 3) a C2-8 alkynyl group, 4) a nitro group, 5) a cyano group, 6) a C1-8 alkyl group substituted by a hydroxy group or a C1-8 alkoxy group, 7) a phenyl group, 8) a group $-C(O)R^8$, 9) a group $-SO_2NR^9R^{10}$, 10) a group $-NR^{11}SO_2R^{12}$, 11) a group $-NR^{13}C(O)R^{14}$ or 12) a group $-CH=NR^{15}$. R^6 and R^7 denote i) a hydrogen atom, ii) a C1-8 alkyl group, iii) a C1-8 alkyl group substituted by a C1-8 alkoxy group, iv) a trihalomethyl group, v) a C3-7 cycloalkyl group, vi) a C1-8 alkyl group substituted by a phenyl group or vii) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^2 denotes 1) a hydrogen atom or 2) a C1-8 alkoxy group. R^3 denotes 1) a hydrogen atom or 2) a C1-8 alkyl group. R^4 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group, 5) a phenyl group which may be substituted by 1-3 halogen atoms or 6) a 3-15 membered mono-, di- or tricyclic hetero ring containing 1-4 nitrogen atoms, 1-3 oxygen atoms and/or 1-3 sulphur atoms. R^5 denotes 1) a hydrogen atom, 2) a C1-8 alkyl group, 3) a C3-7 cycloalkyl group, 4) a C1-8 alkyl group substituted by a C3-7 cycloalkyl group or 5) a phenyl group which may be substituted by 1-3 substituents. In group R^3, a hydrogen atom is preferred. In group R^4, methyl, ethyl, cyclopropyl, cyclobutyl or cyclopentyl are preferred. The compounds of JP-2002-20386-A are stated as having PDE4 inhibitory activity and as being useful in the prevention and/or treatment of inflammatory diseases and many other diseases.

1,3-Dimethyl-4-(arylamino)-pyrazolo[3,4-b]pyridines with a 5-$C(O)NH_2$ substituent similar or identical to those in JP-2002-20386-A were disclosed as orally active PDE4 inhibitors by authors from Ono Pharmaceutical Co. in: H. Ochiai et al., *Bioorg. Med. Chem. Lett.*, 5th January 2004 issue, vol. 14(1), pp. 29-32 (available on or before 4th December 2003 from the Web version of the journal: "articles in press"). Full papers on these and similar compounds as orally active PDE4 inhibitors are: H. Ochiai et al., *Bioorg. Med. Chem.*, 2004, 12, 4089-4100 (available online 20 June 2004), and H. Ochiai et al., *Chem. Pharm. Bull.*, 2004, 52(9), 1098-1104 (available online 15 June 2004).

EP 0 076 035 A1 (ICI Americas) discloses pyrazolo[3,4-b]pyridine derivatives as central nervous system depressants useful as tranquilisers or ataractic agents for the relief of anxiety and tension states.

The compound cartazolate, ethyl 4-(n-butylamino)-1-ethyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxylate, is known. J.W. Daly et al., *Med. Chem. Res.*, 1994, 4, 293-306 and D. Shi et al., *Drug Development Research*, 1997, 42, 41-56 disclose a series of 4-(amino)substituted 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives, including ethyl 4-cyclopentylamino-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate, and their affinities and antagonist activities at A_1- and A_{2A}-adenosine receptors, and the latter paper discloses their affinities at various binding sites of the $GABA_A$-receptor channel. S. Schenone et al., *Bioorg. Med. Chem. Lett.*, 2001, 11, 2529-2531, and F. Bondavalli et al., *J. Med. Chem.*, 2002, vol. 45 (Issue 22, 24 October 2002, allegedly published on Web 09/24/2002), pp. 4875-4887 disclose a series of 4-amino-1-(2-chloro-2-phenylethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl esters as A_1-adenosine receptor ligands.

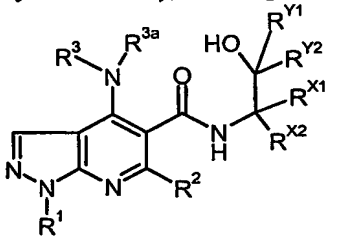
WO 02/060900 A2 appears to disclose, as MCP-1 antagonists for treatment of allergic, inflammatory or autoimmune disorders or diseases, a series of bicyclic heterocyclic compounds with a -C(O)-NR^4-C(O)-NR^5R^6 substituent, including isoxazolo[5,4-b]pyridines and 1*H*-pyrazolo[3,4-b]pyridines (named as pyrazolo[5,4-b]pyridines) with the -C(O)-NR^4-C(O)-NR^5R^6 group as the 5-substituent and optionally substituted at the 1-, 3-, 4-, and/or 6-positions. Bicyclic heterocyclic compounds with a $-C(O)NH_2$ substituent instead of the -C(O)-NR^4-C(O)-NR^5R^6 substituent are alleged to be disclosed in WO 02/060900 as intermediates in the synthesis of the -C(O)-NR^4-C(O)-NR^5R^6 substituted compounds.

WO 00/15222 (Bristol-Myers Squibb) discloses *inter alia* pyrazolo[3,4-b]pyridines having *inter alia* a C(O)-X_1 group at the 5-position and a group E_1 at the 4-position of the ring system. Amongst other things, X_1 can for example be -OR_9, -N(R_9)(R_{10}) or -N(R_5)(-A_2-R_2), and E_1 can for example be -NH-A_1-cycloalkyl, -NH-A_1-substituted cycloalkyl, or -NH-A_1-heterocyclo; wherein A_1 is an alkylene or substituted alkylene bridge of 1 to 10 carbons and A_2 can for example be a direct bond or an alkylene or substituted alkylene bridge of 1 to 10 carbons. The compounds are disclosed as being useful as inhibitors of cGMP phosphodiesterase, especially PDE type V, and in the treatment of various cGMP-associated conditions such as erectile dysfunction. Compounds with a cycloalkyl or heterocyclo group directly attached to -NH- at the 4-position of the pyrazolo[3,4-b]pyridine ring system and/or having PDE4 inhibitory activity do not appear to be disclosed in WO 00/15222.

H. de Mello, A. Echevarria, et al., *J. Med. Chem.*, 2004, believed to be published online on or just before 21 September 2004, discloses 3-methyl or 3-phenyl 4-anilino-1H-pyrazolo[3,4-b]pyridine 5-carboxylic esters as potential anti-*Leishmania* drugs.

Copending patent application PCT/EP2003/014867, filed on 19 December 2003 in the name of Glaxo Group Limited, published on 8 July 2004 as WO 2004/056823 A1, and incorporated herein by reference, discloses and claims pyrazolo[3,4-b]pyridine

compounds or salts thereof with a 4-NR^3R^{3a} group (R^{3a} is preferably H) and with a group Het at the 5-position of the pyrazolo[3,4-b]pyridine, wherein Het is usually a 5-membered optionally substituted heteroaryl group. PCT/EP2003/014867 also discloses the use of these compounds as PDE4 inhibitors and for the treatment and/or prophylaxis of *inter alia* COPD, asthma or allergic rhinitis. In "Process F", on page 58 line 14 to page 59 line 18 of PCT/EP2003/014867 (this passage, plus all definitions elsewhere therein of all compounds, groups and/or substituents mentioned in this passage, being specifically incorporated herein by reference), a compound of general Formula XXVIII:

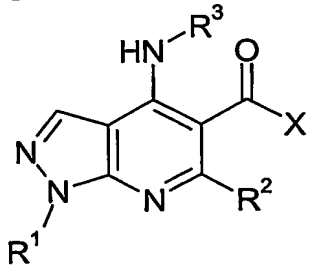


(XXVIII)

is disclosed for use as an intermediate in the synthesis of a subset of the 5-Het pyrazolo[3,4-b]pyridine compounds claimed in PCT/EP2003/014867 wherein Het is optionally substituted 1,3-oxazol-2-yl. Intermediates 42, 43 and 46 within PCT/EP2003/014867 (WO 2004/056823 A1) also disclose embodiments of the compound of Formula XXVIII as intermediate compounds intended for use in the synthesis of the Examples within PCT/EP2003/014867.

Priority is claimed in the present patent application from PCT/EP2003/014867 filed on 19 December 2003, in particular relying on the above-mentioned passages disclosing a compound of Formula XXVIII wherein R^{3a} is preferably H.

Copending patent application PCT/EP03/11814, filed on 12 September 2003 in the name of Glaxo Group Limited, published on 25 March 2004 as WO 2004/024728 A2, and incorporated herein by reference, discloses pyrazolo[3,4-b]pyridine compounds or salts thereof with a 4-NHR^3 group and a 5-C(O)-X group, according to this formula (I):



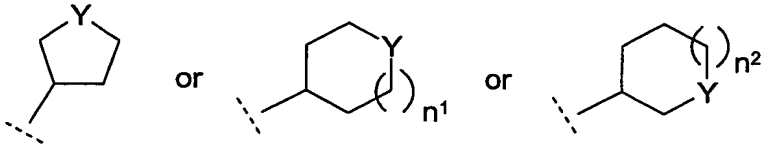
(I)

wherein:

R^1 is C_{1-4}alkyl, C_{1-3}fluoroalkyl, $-CH_2CH_2OH$ or $-CH_2CH_2CO_2C_{1-2}$alkyl;

R^2 is a hydrogen atom (H), methyl or C_1fluoroalkyl;

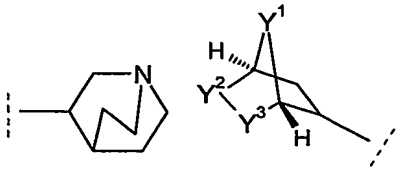
R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc);



(aa) (bb) (cc)

in which n^1 and n^2 independently are 1 or 2; and in which Y is O, S, SO_2, or NR^{10};

or R^3 is a bicyclic group (dd) or (ee):



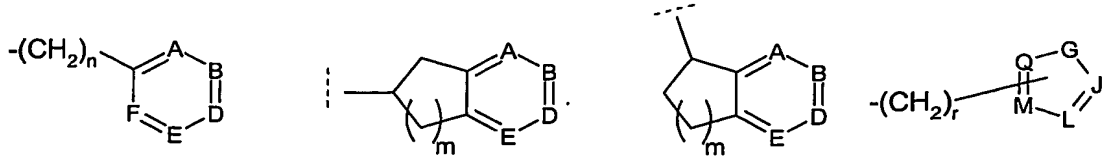
(dd) (ee) ;

and wherein X is NR^4R^5 or OR^{5a}.

In PCT/EP03/11814 (WO 2004/024728 A2), R^4 is a hydrogen atom (H); C_{1-6}alkyl; C_{1-3}fluoroalkyl; or C_{2-6}alkyl substituted by one substituent R^{11}.

In PCT/EP03/11814 (WO 2004/024728 A2), R^5 can be: a hydrogen atom (H); C_{1-8}alkyl; C_{1-8} fluoroalkyl; C_{3-8}cycloalkyl optionally substituted by a C_{1-2}alkyl group; $-(CH_2)_n{}^4$-C_{3-8}cycloalkyl optionally substituted, in the $-(CH_2)_n{}^4$- moiety or in the C_{3-8}cycloalkyl moiety, by a C_{1-2}alkyl group, wherein n^4 is 1, 2 or 3; C_{2-6}alkyl substituted by one or two independent substituents R^{11}; $-(CH_2)_n{}^{11}$-$C(O)R^{16}$; $-(CH_2)_n{}^{12}$-$C(O)NR^{12}R^{13}$; $-CHR^{19}$-$C(O)NR^{12}R^{13}$; $-(CH_2)_n{}^{12}$-$C(O)OR^{16}$; $-(CH_2)_n{}^{12}$-C(O)OH; $-CHR^{19}$-$C(O)OR^{16}$; $-CHR^{19}$-C(O)OH; $-(CH_2)_n{}^{12}$-SO_2-$NR^{12}R^{13}$; $-(CH_2)_n{}^{12}$-SO_2R^{16}; or $-(CH_2)_n{}^{12}$-CN; $-(CH_2)_n{}^{13}$-Het; or optionally substituted phenyl.

Alternatively, in PCT/EP03/11814 (WO 2004/024728 A2), R^5 can have the sub-formula (x), (y), (y1) or (z):



(x) (y) (y1) (z)

wherein in sub-formula (x), n = 0, 1 or 2; in sub-formula (y) and (y1), m = 1 or 2; and in sub-formula (z), r = 0, 1 or 2; and wherein in sub-formula (x) and (y) and (y1), none, one or two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-) provided that no more than one of A, B, D, E and F is nitrogen-oxide, and the remaining of A, B, D, E and F are independently CH or CR^6; and provided that when n is 0 in sub-formula (x) then one or two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-) and no more than one of A, B, D, E and F is nitrogen-oxide;

In PCT/EP03/11814 (WO 2004/024728 A2), each R^6, independently of any other R^6 present, is: a halogen atom; C_{1-6}alkyl; C_{1-4}fluoroalkyl; C_{1-4}alkoxy; C_{1-2}fluoroalkoxy; C_{3-6}cycloalkyloxy; -C(O)R^{16a}; -C(O)OR^{30}; -S(O)$_2$-R^{16a}; R^{16a}-S(O)$_2$-NR^{15a}-; R^7R^8N-S(O)$_2$-; C_{1-2}alkyl-C(O)-R^{15a}N-S(O)$_2$-; C_{1-4}alkyl-S(O)-; Ph-S(O)-; R^7R^8N-CO-; -NR^{15}-C(O)R^{16}; R^7R^8N; OH; C_{1-4}alkoxymethyl; C_{1-4}alkoxyethyl; C_{1-2}alkyl-S(O)$_2$-CH_2-; R^7R^8N-S(O)$_2$-CH_2-; C_{1-2}alkyl-S(O)$_2$-NR^{15a}-CH_2-; -CH_2-OH; -CH_2CH_2-OH; -CH_2-NR^7R^8; -CH_2-CH_2-NR^7R^8; -CH_2-C(O)OR^{30}; -CH_2-C(O)-NR^7R^8; -CH_2-NR^{15a}-C(O)-C_{1-3}alkyl; -$(CH_2)_n{}^{14}$-Het^1 where n^{14} is 0 or 1; cyano (CN); Ar^{5b}; or phenyl, pyridinyl or pyrimidinyl wherein the phenyl, pyridinyl or pyrimidinyl independently are optionally substituted by one or two of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

or two adjacent R^6 taken together can be –O–(CMe_2)–O– or –O–$(CH_2)_n{}^{14}$–O– where n^{14} is 1 or 2.

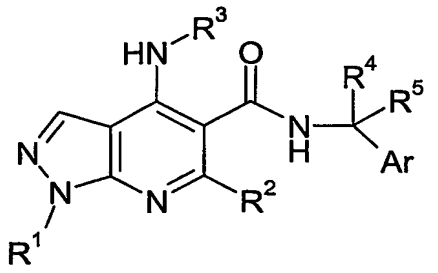
In PCT/EP03/11814 (WO 2004/024728 A2), in sub-formula (z), G is O or S or NR^9 wherein R^9 is a hydrogen atom (H), C_{1-4}alkyl or C_{1-4}fluoroalkyl; none, one, two or three of J, L, M and Q are nitrogen; and the remaining of J, L, M and Q are independently CH or CR^6 where R^6, independently of any other R^6 present, is as defined therein.

The pyrazolo[3,4-b]pyridine compounds of formula (I) and salts thereof disclosed in PCT/EP03/11814 (WO 2004/024728 A2) are disclosed as being inhibitors of phosphodiesterase type IV (PDE4), and as being useful for the treatment and/or prophylaxis of an inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis, or allergic rhinitis.

The Invention

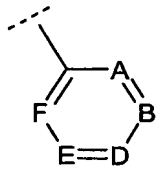
We have now found new pyrazolo[3,4-b]pyridine compounds, having a -C(O)-NH-C(R^4)(R^5)-aryl substituent at the 5-position of the pyrazolo[3,4-b]pyridine ring system wherein at least one of R^4 and R^5 is not a hydrogen atom (H), which compounds inhibit phosphodiesterase type IV (PDE4).

The present invention therefore provides a compound of formula (I) or a salt thereof (in particular, a pharmaceutically acceptable salt thereof):

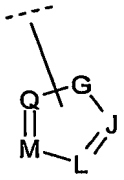


(I)

wherein Ar has the sub-formula (x) or (z):



(x)



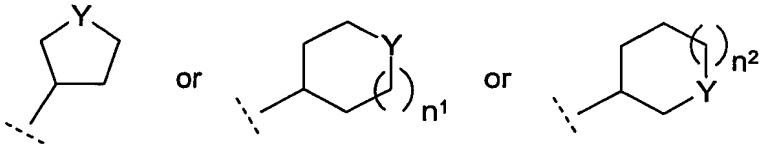
(z)

and wherein:

R^1 is C_{1-3}alkyl, C_{1-3}fluoroalkyl, or -CH_2CH_2OH;

R^2 is a hydrogen atom (H), methyl or C_1fluoroalkyl;

R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc);

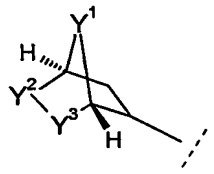


(aa) (bb) (cc)

in which n^1 and n^2 independently are 1 or 2; and in which Y is O, S, SO_2, or NR^{10}; where R^{10} is a hydrogen atom (H), C_{1-2}alkyl, C_{1-2}fluoroalkyl, $C(O)NH_2$, $C(O)$-C_{1-2}alkyl, $C(O)$-C_1fluoroalkyl or -$C(O)$-CH_2O-C_1alkyl;

and wherein in R^3 the C_{3-8}cycloalkyl or the heterocyclic group of sub-formula (aa), (bb) or (cc) is optionally substituted on a ring carbon with one or two substituents independently being oxo (=O); OH; C_{1-2}alkoxy; C_{1-2}fluoroalkoxy; NHR^{21} wherein R^{21} is a hydrogen atom (H) or C_{1-4} straight-chain alkyl; C_{1-2}alkyl; C_{1-2}fluoroalkyl; -CH_2OH; -CH_2CH_2OH; -CH_2NHR^{22} wherein R^{22} is H or C_1alkyl; -$C(O)OR^{23}$ wherein R^{23} is H; -$C(O)NHR^{24}$ wherein R^{24} is H or C_1alkyl; -$C(O)R^{25}$ wherein R^{25} is C_{1-2}alkyl; fluoro; hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-4}alkyl); and wherein any OH, alkoxy, fluoroalkoxy or NHR^{21} substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc);

and wherein, when R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, then the cycloalkenyl is optionally substituted with one substituent being fluoro or C_{1-2}alkyl or two substituents independently being fluoro or methyl , and the R^3 ring carbon bonded to the -NH- group of formula (I) does not partake in the cycloalkenyl double bond;



(ee)

or R^3 is a bicyclic group of sub-formula (ee): wherein Y^1, Y^2 and Y^3 independently are CH_2 or oxygen (O) provided that no more than one of Y^1, Y^2 and Y^3 is oxygen (O);

and wherein:

R^4 is a hydrogen atom (H), methyl, ethyl, n-propyl, isopropyl, C_{1-2}fluoroalkyl, cyclopropyl, -CH_2OR^{4a}, -$CH(Me)OR^{4a}$, or -$CH_2CH_2OR^{4a}$; wherein R^{4a} is a hydrogen atom (H), methyl (Me), or C_1fluoroalkyl such as CF_3 or CHF_2; and

R^5 is a hydrogen atom (H); C_{1-8}alkyl (e.g. C_{1-6}alkyl or C_{1-4}alkyl); C_{1-3}fluoroalkyl; C_{3-8}cycloalkyl optionally substituted by a C_{1-2}alkyl group; or -$(CH_2)_n^4$-C_{3-8}cycloalkyl optionally substituted, in the -$(CH_2)_n^4$- moiety or in the C_{3-8}cycloalkyl moiety, by a C_{1-2}alkyl group, wherein n^4 is 1 or 2;

or R^5 is C_{1-4}alkyl substituted by one substituent R^{11}; wherein R^{11} is: hydroxy (OH); C_{1-6}alkoxy; C_{1-2}fluoroalkoxy; phenyloxy; (monofluoro- or difluoro-phenyl)oxy; (monomethyl- or dimethyl-phenyl)oxy; benzyloxy; -$NR^{12}R^{13}$; -NR^{15}-$C(O)R^{16}$; -NR^{15}-C(O)-NH-R^{15}; or -NR^{15}-$S(O)_2R^{16}$;

or R^5 is C_{2-4}alkyl substituted on different carbon atoms by two hydroxy (OH) substituents;

or R^5 is -$(CH_2)_n^{11}$-$C(O)R^{16}$; -$(CH_2)_n^{11}$-$C(O)NR^{12}R^{13}$; -CHR^{19}-$C(O)NR^{12}R^{13}$; -$(CH_2)_n^{11}$-$C(O)OR^{16}$; -$(CH_2)_n^{11}$-C(O)OH; -CHR^{19}-$C(O)OR^{16}$; -CHR^{19}-C(O)OH; -$(CH_2)_n^{11}$-$S(O)_2$-$NR^{12}R^{13}$; -$(CH_2)_n^{11}$-$S(O)_2R^{16}$; or -$(CH_2)_n^{11}$-CN; wherein n^{11} is 0, 1, 2 or 3 (wherein for each R^5 group n^{11} is independent of the value of n^{11} in other R^5 groups); and wherein R^{19} is C_{1-2}alkyl;

or R^5 is -$(CH_2)_n^{13}$-Het, wherein n^{13} is 0, 1 or 2 and Het is a 4-, 5-, 6- or 7-membered saturated or unsaturated heterocyclic ring, other than -$NR^{12}R^{13}$, containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-hetero-atoms present are not bound to the -$(CH_2)_n^{13}$- moiety when n^{13} is 0; wherein any ring-nitrogens which are present and which are not unsaturated (i.e. which do not partake in a double bond) and which are not connecting nitrogens (i.e. which are not nitrogens bound to the -$(CH_2)_n^{13}$- moiety or to the carbon atom to which R^5 is attached) are present as NR^{17}; and wherein one or two of the carbon ring-atoms are independently optionally substituted by C_{1-2}alkyl;

or R^5 is phenyl (Ph), -CH_2-Ph, -CHMe-Ph, -CHEt-Ph, CMe_2Ph, or -CH_2CH_2-Ph, wherein the phenyl ring Ph is optionally substituted with one or two substituents independently being: a halogen atom; C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-2}fluoroalkyl (e.g. trifluoromethyl); C_{1-4}alkoxy (e.g. C_{1-2}alkoxy); C_{1-2}fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy); cyclopropyl; cyclopropyloxy; -C(O)-C_{1-4}alkyl; -C(O)OH; -C(O)-OC_{1-4}alkyl; C_{1-4}alkyl-$S(O)_2$-; C_{1-4}alkyl-$S(O)_2$-NR^{8a}-; $R^{7a}R^{8a}$N-$S(O)_2$-; $R^{7a}R^{8a}$N-C(O)-; -NR^{8a}-C(O)-C_{1-4}alkyl; $R^{7a}R^{8a}$N; OH; nitro (-NO_2); or cyano (-CN);

or R^4 and R^5 taken together are $-(CH_2)_p{}^1-$ or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$, in which: X^5 is O or NR^{17a}; $p^1 = 2, 3, 4, 5$ or 6, and p^3 and p^4 independently are 1, 2 or 3 provided that if p^3 is 3 then p^4 is 1 or 2 and if p^4 is 3 then p^3 is 1 or 2;

provided that at least one of R^4 and R^5 is not a hydrogen atom (H);

and wherein, in sub-formula (x):

A is C-R^{6A}, nitrogen (N) or nitrogen-oxide (N^+-O^-),
B is C-R^{6B}, nitrogen (N) or nitrogen-oxide (N^+-O^-),
D is C-R^{6D}, nitrogen (N) or nitrogen-oxide (N^+-O^-),
E is C-R^{6E}, nitrogen (N) or nitrogen-oxide (N^+-O^-),
F is C-R^{6F}, nitrogen (N) or nitrogen-oxide (N^+-O^-),

wherein, R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} independently are: a hydrogen atom (H), a halogen atom; C_{1-6}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl); C_{1-4}fluoroalkyl (e.g. C_{1-2}fluoroalkyl); C_{3-6}cycloalkyl; C_{1-4}alkoxy (e.g. C_{1-2}alkoxy); C_{1-2}fluoroalkoxy; C_{3-6}cycloalkyloxy; $-C(O)R^{16a}$; $-C(O)OR^{30}$; $-S(O)_2-R^{16a}$ (e.g. C_{1-2}alkyl-$S(O)_2$-); R^{16a}-$S(O)_2$-NR^{15a}- (e.g. C_{1-2}alkyl-$S(O)_2$-NH-); R^7R^8N-$S(O)_2$-; C_{1-2}alkyl-C(O)-$R^{15a}N$-$S(O)_2$-; C_{1-4}alkyl-S(O)-, Ph-S(O)-, R^7R^8N-CO-; $-NR^{15a}$-$C(O)R^{16a}$; R^7R^8N; nitro ($-NO_2$); OH (including any tautomer thereof); C_{1-4}alkoxymethyl; C_{1-4}alkoxyethyl; C_{1-2}alkyl-$S(O)_2$-CH_2-; R^7R^8N-$S(O)_2$-CH_2-; C_{1-2}alkyl-$S(O)_2$-NR^{15a}-CH_2-; $-CH_2$-OH; $-CH_2CH_2$-OH; $-CH_2-NR^7R^8$; $-CH_2-CH_2-NR^7R^8$; $-CH_2-C(O)OR^{30}$; $-CH_2-C(O)-NR^7R^8$; $-CH_2-NR^{15a}$-C(O)-C_{1-3}alkyl; $-(CH_2)_n{}^{14}$-Het^1 where n^{14} is 0 or 1; cyano (-CN); Ar^{5b}; or phenyl, pyridinyl or pyrimidinyl wherein the phenyl, pyridinyl or pyrimidinyl independently are optionally substituted by one or two of fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

and/or two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are taken together and are: –CH=CH–CH=CH–, $-(CH_2)_n{}^{14a}-$ where n^{14a} is 3, 4 or 5 (e.g. 3 or 4), –O–(CMe_2)–O–, $-O-(CH_2)_n{}^{14b}-O-$ where n^{14b} is 1 or 2; -CH=CH-NR^{15b}-; -N=CH-NR^{15b}-; -CH=N-NR^{15b}-; -N=N-NR^{15b}-; -CH=CH-O-; -N=CH-O-; -CH=CH-S-; or -N=CH-S-; wherein R^{15b} is H or C_{1-2}alkyl;

provided that:

two or more of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), nitrogen (N), or nitrogen-oxide (N^+-O^-);

and no more than two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-),

and no more than one of A, B, D, E and F is nitrogen-oxide (N^+-O^-);

and wherein, in sub-formula (z):

G is O or S or NR^9 wherein R^9 is a hydrogen atom (H), C_{1-4}alkyl, or C_{1-2}fluoroalkyl;
J is C-R^{6J}, C-[connection point to formula (I)], or nitrogen (N),
L is C-R^{6L}, C-[connection point to formula (I)], or nitrogen (N),
M is C-R^{6M}, C-[connection point to formula (I)], or nitrogen (N),
Q is C-R^{6Q}, C-[connection point to formula (I)], or nitrogen (N),

wherein, R^{6J}, R^{6L}, R^{6M} and R^{6Q} independently are: a hydrogen atom (H), a halogen atom; C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-3}fluoroalkyl (e.g. C_{1-2}fluoroalkyl); C_{3-6}cycloalkyl; C_{1-4}alkoxy (e.g. C_{1-2}alkoxy); C_{1-2}fluoroalkoxy; C_{3-6}cycloalkyloxy; OH (including any tautomer thereof); or phenyl optionally substituted by one or two substituents independently being fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

provided that:
two or more of J, L, M and Q are independently C-H, C-F, C-C_{1-2}alkyl (e.g. C-Me), C-[connection point to formula (I)], or nitrogen (N);
and no more than three of J, L, M and Q are nitrogen (N);

and wherein:

R^7 and R^8 are independently a hydrogen atom (H); C_{1-4}alkyl (e.g. C_{1-2}alkyl such as methyl); C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two substituents independently being: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

or R^7 and R^8 together are -$(CH_2)_n{}^6$- or -C(O)-$(CH_2)_n{}^7$- or -C(O)-$(CH_2)_n{}^{10}$-C(O)- or -$(CH_2)_n{}^8$-X^7-$(CH_2)_n{}^9$- or -C(O)-X^7-$(CH_2)_n{}^{10}$- in which: n^6 is 3, 4, 5 or 6, n^7 is 2, 3, 4, or 5, n^8 and n^9 and n^{10} independently are 2 or 3, and X^7 is O or NR^{14};

R^{7a} is a hydrogen atom (H) or C_{1-4}alkyl;

R^{8a} is a hydrogen atom (H) or methyl;

R^{12} and R^{13} independently are H; C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two substituents independently being: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

or R^{12} and R^{13} together are $-(CH_2)_n{}^{6a}-$ or $-C(O)-(CH_2)_n{}^{7a}-$ or $-C(O)-(CH_2)_n{}^{10a}-C(O)-$ or $-(CH_2)_n{}^{8a}-X^{12}-(CH_2)_n{}^{9a}-$ or $-C(O)-X^{12}-(CH_2)_n{}^{10a}-$ in which: n^{6a} is 3, 4, 5 or 6, n^{7a} is 2, 3, 4, or 5, n^{8a} and n^{9a} and n^{10a} independently are 2 or 3 and X^{12} is O or NR^{14a};

R^{14}, R^{14a}, R^{17} and R^{17a} independently are: a hydrogen atom (H); C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{1-2}fluoroalkyl (e.g. CF_3); cyclopropyl; $-C(O)-C_{1-4}$alkyl (e.g. -C(O)Me); $-C(O)NR^{7a}R^{8a}$ (e.g. $-C(O)NH_2$); or $-S(O)_2-C_{1-4}$alkyl (e.g. $-S(O)_2Me$);

R^{15}, independent of other R^{15}, is a hydrogen atom (H); C_{1-4}alkyl (e.g. ^{t}Bu or C_{1-2}alkyl e.g. methyl); C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

R^{15a}, independent of other R^{15a}, is a hydrogen atom (H) or C_{1-4}alkyl;

R^{16} is: C_{1-4}alkyl (e.g. C_{1-2}alkyl); C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl); C_{3-6}cycloalkyl-CH_2- (e.g. C_{5-6}cycloalkyl-CH_2-); or phenyl or benzyl, wherein the phenyl and benzyl are independently optionally substituted on their ring by one or two substituents independently being fluoro, chloro, methyl, C_1fluoroalkyl, methoxy or C_1fluoroalkoxy;

R^{16a} is:
C_{1-6}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl);
C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl) optionally substituted by one oxo (=O), OH or C_{1-2}alkyl substituent (e.g. optionally substituted at the 3- or 4-position of a C_{5-6}cycloalkyl ring; and/or preferably unsubstituted C_{3-6}cycloalkyl);
C_{3-6}cycloalkyl-CH_2- (e.g. C_{5-6}cycloalkyl-CH_2-);
pyridinyl (e.g. pyridin-2-yl) optionally substituted on a ring carbon atom by one of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;
Ar^{5c};
phenyl optionally substituted by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;

benzyl optionally substituted on its ring by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or

a 4-, 5-, 6- or 7-membered saturated heterocyclic ring connected at a ring-carbon and containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-nitrogens which are present are present as NR^{27} where R^{27} is H, C_{1-2}alkyl or -C(O)Me; and wherein the ring is optionally substituted at carbon by one C_{1-2}alkyl or oxo (=O) substituent, provided that any oxo (=O) substituent is substituted at a ring-carbon atom bonded to a ring-nitrogen;

R^{30}, independent of other R^{30}, is a hydrogen atom (H), C_{1-4}alkyl or C_{3-6}cycloalkyl;

Ar^{5b} and Ar^{5c} independently is/are a 5-membered aromatic heterocyclic ring containing one O, S or NR^{15a} in the 5-membered ring, wherein the 5-membered ring can optionally additionally contain one or two N atoms, and wherein the heterocyclic ring is optionally substituted on a ring carbon atom by one of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, $-CH_2OH$, $-CH_2-OC_{1-2}$alkyl, OH (including the keto tautomer thereof) or $-CH_2-NR^{28}R^{29}$ wherein R^{28} and R^{29} independently are H or methyl; and

Het^1 , is a 4-, 5-, 6- or 7-membered saturated heterocyclic ring connected at a ring-carbon and containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-nitrogens which are present are present as NR^{31} where R^{31} is H, C_{1-2}alkyl or -C(O)Me; and wherein the ring is optionally substituted at carbon by one C_{1-2}alkyl or oxo (=O) substituent, provided that any oxo (=O) substituent is substituted at a ring-carbon atom bonded to a ring-nitrogen;

provided that:
when R^3 is the heterocyclic group of sub-formula (bb), n^1 is 1, and Y is NR^{10}, then R^{10} is not C_{1-2}alkyl or C_{1-2}fluoroalkyl; and

when R^3 is the heterocyclic group of sub-formula (aa) and Y is NR^{10}, then R^{10} is not C(O)-C_{1-2}alkyl, C(O)-C_1fluoroalkyl or -C(O)-CH_2O-C_1alkyl; and

when R^3 is the heterocyclic group of sub-formula (cc), then Y is O, S, SO_2 or NR^{10} wherein R^{10} is H;

and provided that:
when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, then any $-C(O)OR^{23}$, $-C(O)NHR^{24}$, $-C(O)R^{25}$, $-CH_2OH$ or fluoro substituent is: at the 3-position of a R^3 cyclobutyl ring; or at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) or cyclopentenyl ring; or at the 4-position of a R^3 C_6cycloalkyl (cyclohexyl) or cyclohexenyl ring; or at the 3-, 4-, 5- or 6- position of a R^3

cycloheptyl or cycloheptenyl ring, or at the 3-, 4-, 5-, 6- or 7- position of a R^3 cyclooctyl ring (wherein, in this connection, the 1-position of the R^3 cycloalkyl or cycloalkenyl ring is deemed to be the connection point to the -NH- in formula (I), that is the ring atom connecting to the -NH- in formula (I));

and provided that:
when R^3 is optionally substituted C_{3-8}cycloalkyl, then any OH, alkoxy, fluoroalkoxy, $-CH_2CH_2OH$ or $-CH_2NHR^{22}$ substituent is: at the 3-position of a R^3 cyclobutyl ring; or at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) ring; or at the 3-, 4- or 5- position of a R^3 C_6cycloalkyl (cyclohexyl) ring; or at the 3-, 4-, 5- or 6- position of a R^3 cycloheptyl ring, or at the 3-, 4-, 5-, 6- or 7- position of a R^3 cyclooctyl ring; and

when R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then any OH substituent is: at the 5-position of a six-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 1; or at the 5- or 6- position of a seven-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 2; or at the 6- position of a seven-membered R^3 heterocyclic group of sub-formula (bb) wherein n^1 is 2 (wherein, in this connection, the 1-position of the R^3 heterocyclic ring is deemed to be the connection point to the -NH- in formula (I), that is the ring atom connecting to the -NH- in formula (I), and the remaining positions of the ring are then numbered so that the ring heteroatom takes the lowest possible number).

In compounds, for example in the compounds of formula (I) (or formula (IA) or formula (IB), see later), an "alkyl" group or moiety may be straight-chain or branched. Alkyl groups, for example C_{1-8}alkyl or C_{1-6}alkyl or C_{1-4}alkyl or C_{1-3}alkyl or C_{1-2}alkyl, which may be employed include C_{1-6}alkyl or C_{1-4}alkyl or C_{1-3}alkyl or C_{1-2}alkyl such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, or n-hexyl or any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, isobutyl, 3-methylbutan-2-yl, 2-ethylbutan-1-yl, or the like.

A corresponding meaning is intended for "alkoxy", "alkylene", and like terms derived from alkyl. For example, "alkoxy" such as C_{1-6}alkoxy or C_{1-4}alkoxy or C_{1-2}alkoxy includes methoxy, ethoxy, propyloxy, and oxy derivatives of the alkyls listed above. "Alkylsulfonyl" such as C_{1-4}alkylsulfonyl includes methylsulfonyl (methanesulfonyl), ethylsulfonyl, and others derived from the alkyls listed above. "Alkylsulfonyloxy" such as C_{1-4}alkylsulfonyloxy includes methanesulfonyloxy (methylsulfonyloxy), ethanesulfonyloxy, *et al.*

"Cycloalkyl", for example C_{3-8}cycloalkyl, includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Suitably, a

C_{3-8}cycloalkyl group can be C_{3-6}cycloalkyl or C_{5-6}cycloalkyl or C_{4-7}cycloalkyl or C_{6-7}cycloalkyl, that is contains a 3-6 membered or 5-6 membered or 4-7 membered or 6-7 membered carbocyclic ring.

"Fluoroalkyl" includes alkyl groups with one, two, three, four, five or more fluorine substituents, for example C_{1-4}fluoroalkyl or C_{1-3}fluoroalkyl or C_{1-2}fluoroalkyl such as monofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl (CF_3CH_2-), 2,2-difluoroethyl (CHF_2CH_2-), 2-fluoroethyl (CH_2FCH_2-), etc. "Fluoroalkoxy" includes C_{1-4}fluoroalkoxy or C_{1-2}fluoroalkoxy such as trifluoromethoxy, pentafluoroethoxy, monofluoromethoxy, difluoromethoxy, etc. "Fluoroalkylsulfonyl" such as C_{1-4}fluoroalkylsulfonyl includes trifluoromethanesulfonyl, pentafluoroethylsulfonyl, etc.

A halogen atom ("halo") present in compounds, for example in the compounds of formula (I), means a fluorine, chlorine, bromine or iodine atom ("fluoro", "chloro", "bromo" or "iodo"), for example fluoro, chloro or bromo.

When the specification states that atom or moiety A is "bonded" or "attached" to atom or moiety B, it means that atom/moiety A is directly bonded to atom/moiety B usually by means of a covalent bond or a double covalent bond, and excludes A being indirectly attached to B via one or more intermediate atoms/moieties (e.g. excludes A-C-B); unless it is clear from the context that another meaning is intended.

When R^1 is C_{1-3}alkyl or C_{1-3}fluoroalkyl, it can be straight-chained or branched. Where R^1 is C_{1-3}alkyl then it can be methyl, ethyl, n-propyl, or isopropyl. When R^1 is C_{1-3}fluoroalkyl, then R^1 can for example be C_1fluoroalkyl such as monofluoromethyl, difluoromethyl, trifluoromethyl; or R^1 can be C_2fluoroalkyl such as pentafluoroethyl or more preferably C_1fluoroalkyl-CH_2- such as 2,2,2-trifluoroethyl (CF_3CH_2-), 2,2-difluoroethyl (CHF_2CH_2-), or 2-fluoroethyl (CH_2FCH_2-).

R^1 is C_{1-3}alkyl (e.g. methyl, ethyl or n-propyl), C_{1-3}fluoroalkyl or -CH_2CH_2OH. R^1 is suitably C_{1-3}alkyl, C_{1-2}fluoroalkyl, or -CH_2CH_2OH. Preferably, R^1 is C_{2-3}alkyl (e.g. ethyl or n-propyl), C_2fluoroalkyl (e.g. C_1fluoroalkyl-CH_2- such as CF_3-CH_2-) or -CH_2CH_2OH; in particular ethyl, n-propyl or -CH_2CH_2OH. More preferably, R^1 is C_2alkyl (ethyl) or C_2fluoroalkyl. R^1 is most preferably ethyl.

Preferably, R^2 is a hydrogen atom (H) or methyl, for example a hydrogen atom (H).

Preferably, in R^3 there is one substituent or no substituent.

In one suitable embodiment, R^3 is the optionally substituted C_{3-8}cycloalkyl or the optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc).

In one optional embodiment, when R^3 is optionally substituted C_{3-8}cycloalkyl, it is not unsubstituted C_5cycloalkyl, i.e. not unsubstituted cyclopentyl. In this case, suitably, R^3 is optionally substituted C_{6-8}cycloalkyl or optionally substituted cyclobutyl.

When R^3 is optionally substituted C_{3-8}cycloalkyl, it is more suitably optionally substituted C_{6-7}cycloalkyl or optionally substituted cyclobutyl, preferably optionally substituted C_6cycloalkyl (i.e. optionally substituted cyclohexyl).

Suitably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl or cyclobutyl) optionally substituted with one or two substituents independently being oxo (=O); OH; C_1alkoxy; C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy); NHR^{21} wherein R^{21} is a hydrogen atom (H) or C_{1-2}alkyl (more preferably R^{21} is H); C_{1-2}alkyl such as methyl; C_1fluoroalkyl such as $-CH_2F$ or $-CHF_2$; $-CH_2OH$; $-CH_2NHR^{22}$ wherein R^{22} is H; $-C(O)OR^{23}$ wherein R^{23} is H; $-C(O)NHR^{24}$ wherein R^{24} is H or methyl; $-C(O)R^{25}$ wherein R^{25} is methyl; fluoro; hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino such as (C_{1-2}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-4}alkyl such as C_{1-2}alkyl); and wherein any OH, alkoxy, fluoroalkoxy or NHR^{21} substituent is not substituted at the R^3 ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either R^3 ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc).

Preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl or cyclobutyl) optionally substituted with one or two substituents independently being oxo (=O); OH; NHR^{21} wherein R^{21} is a hydrogen atom (H); C_{1-2}alkyl such as methyl; C_1fluoroalkyl such as $-CH_2F$ or $-CHF_2$; $-C(O)OR^{23}$ wherein R^{23} is H; $-C(O)NHR^{24}$ wherein R^{24} is H or methyl (preferably H); $-C(O)R^{25}$ wherein R^{25} is methyl; fluoro; hydroxyimino (=N-OH); or (C_{1-2}alkoxy)imino (=N-OR^{26} where R^{26} is C_{1-2}alkyl).

More preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl or cyclobutyl) optionally substituted with one or two substituents independently being (e.g. one substituent being) oxo (=O); OH; NHR^{21} wherein R^{21} is a hydrogen atom (H); methyl; $-CH_2F$; $-CHF_2$; $-C(O)OR^{23}$ wherein R^{23} is H; $-C(O)NHR^{24}$ wherein R^{24} is H or methyl (preferably H); fluoro; hydroxyimino (=N-OH); or methoxyimino (=N-OR^{26} where R^{26} is methyl).

Still more preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl or cyclobutyl) optionally substituted with one or two substituents independently being (e.g. one substituent being) oxo (=O); OH; methyl; -C(O)NHR^{24} wherein R^{24} is H; fluoro; hydroxyimino (=N-OH); or methoxyimino (=N-OR^{26} where R^{26} is methyl).

Yet more preferably, when R^3 is optionally substituted C_{3-8}cycloalkyl, then R^3 is C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl or cyclobutyl) optionally substituted with one or two substituents independently being (e.g. one substituent being) OH; -C(O)NHR^{24} wherein R^{24} is H; oxo (=O) or hydroxyimino (=N-OH).

In one optional embodiment, in R^3, the C_{3-8}cycloalkyl can be unsubstituted.

When R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, e.g. optionally substituted C_{5-8}cycloalkyl or C_{5-7}cycloalkyl, such as optionally substituted C_6cycloalkyl (optionally substituted cyclohexyl) or optionally substituted cyclohexenyl, the one or two optional substituents if present suitably can comprise a substituent (for example is or are substituent(s)) at the 3-, 4- and/or 5-position(s), e.g. at the 3- and/or 4- position(s), of the R^3 cycloalkyl or cycloalkenyl ring.

(In this connection and generally herein, the 1-position of the R^3 ring, e.g. of the R^3 cycloalkyl or cycloalkenyl ring, is deemed to be the connection point to the -NH- in formula (I) = the ring atom connecting to the -NH- in formula (I)).

Suitably, for R^3, and in particular when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, R^3 is not substituted (other than optionally by alkyl or fluoroalkyl) at the ring atom connecting to the -NH- in formula (I), and R^3 is not substituted (other than optionally by alkyl, fluoroalkyl or NHR^{21}) at the two ring atoms either side of (bonded to) the connecting atom. For example, suitably, for R^3, and in particular when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, R^3 is not substituted at the ring atom connecting to the -NH- in formula (I), and R^3 is not substituted at the two ring atoms either side of (bonded to) the connecting atom.

Suitably, for R^3, and in particular when R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, the one or two optional R^3 substituents if present can comprise a substituent (for example is or are substituent(s)):
(a) at the 3-position of a R^3 cyclobutyl ring, or
(b) at the 3- and/or 4- position(s) of a R^3 cyclopentyl or cyclopentenyl ring, or

(c) at the 3-, 4- and/or 5- position(s) of a R^3 cyclohexyl or cyclohexenyl ring, or
(d) at the 3-, 4-, 5- and/or 6- position(s) of a R^3 cycloheptyl or cycloheptenyl ring, or
(e) at the 3-, 4-, 5-, 6- and/or 7- position(s) of a R^3 cyclooctyl ring,
and/or
(f) at the 1-, 2- and/or highest-numbered- position(s) of a R^3 cycloalkyl or cycloalkenyl ring, for alkyl or fluoroalkyl substituent(s), and/or
(g) at the 2- and/or highest-numbered- position(s) of a R^3 cycloalkyl or cycloalkenyl ring, for NHR^{21} substituent(s).

When R^3 is optionally substituted C_{3-8}cycloalkyl, any OH, alkoxy, fluoroalkoxy, $-CH_2CH_2OH$ or $-CH_2NHR^{22}$ substituent (particularly any OH substituent) is suitably at the 3-, 4- or 5- position, e.g. 3- or 5-position, of the R^3 cycloalkyl (e.g. C_{6-8}cycloalkyl) ring. Optionally, any OH, alkoxy, fluoroalkoxy, $-CH_2CH_2OH$ or $-CH_2NHR^{22}$ substituent (particularly any OH substituent) can be: at the 3-position of a R^3 cyclobutyl ring; or at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) ring; or at the 3-, 4- or 5- position of a R^3 C_6cycloalkyl (cyclohexyl) ring (e.g. at the 3- or 5-position of a R^3 cyclohexyl ring especially for any OH substituent); or at the 3-, 4-, 5- or 6- position of a R^3 cycloheptyl ring, or at the 3-, 4-, 5-, 6- or 7- position of a R^3 cyclooctyl ring. Suitably, any OH, alkoxy, fluoroalkoxy, $-CH_2CH_2OH$ or $-CH_2NHR^{22}$ substituent (particularly any OH substituent) is at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) ring; or more suitably at the 3-, 4- or 5- position, still more suitably at the 3- or 5-position, of a R^3 C_6cycloalkyl (cyclohexyl) ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, then any $-C(O)OR^{23}$, $-C(O)NHR^{24}$, $-C(O)R^{25}$, $-CH_2OH$ or fluoro substituent is: at the 3-position of a R^3 cyclobutyl ring; or at the 3- or 4- position of a R^3 C_5cycloalkyl (cyclopentyl) or cyclopentenyl ring; or at the 4-position of a R^3 C_6cycloalkyl (cyclohexyl) or cyclohexenyl ring; or at the 3-, 4-, 5- or 6- position of a R^3 cycloheptyl or cycloheptenyl ring, or at the 3-, 4-, 5-, 6- or 7- position of a R^3 cyclooctyl ring. Any $-C(O)OR^{23}$, $-C(O)NHR^{24}$, $-C(O)R^{25}$, $-CH_2OH$ or fluoro substituent, e.g. any $-C(O)NHR^{24}$ or fluoro substituent, is suitably at the 4-position of a R^3 C_6cycloalkyl (cyclohexyl) or cyclohexenyl ring. It is particularly preferable for any $-C(O)NHR^{24}$ substituent to be at the 4-position of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl, any NHR^{21} substituent is at any position other than the 1-position (the ring atom connecting to the -NH- in formula (I)), e.g. at the 2-, 3-, 4-, 5-, 6-, 7- or 8- position. Suitably, any NHR^{21} substituent is at the 2-, 3-, 4-, 5- or 6- position, for example at the 3- or 5- position, of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl or optionally substituted C_{5-7}cycloalkenyl, any alkyl or fluoroalkyl substituent can for example be at the 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8- position, for example at the 1-, 2-, 3-, 5- or 6- position, e.g. the 1-position, of the R^3 ring. Preferably, any alkyl or fluoroalkyl substituent is at the 1-, 2-, 3-, 5- or 6- position, or more preferably at the 1-, 3- or 5- position, of a R^3 cyclohexyl or cyclohexenyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl, any oxo (=O), hydroxyimino (=N-OH); or (C_{1-4}alkoxy)imino (=N-OR^{26}) substituent is suitably at the 3-, 4- or 5-position, e.g. at the 4-position, of the R^3 cycloalkyl (e.g. C_{6-8}cycloalkyl e.g. cyclohexyl) ring. Preferably any such substituent is at the 4-position of a R^3 cyclohexyl ring.

When R^3 is optionally substituted C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl), R^3 is preferably cyclohexyl (i.e. unsubstituted); or cycloheptyl (i.e. unsubstituted); or cyclohexyl substituted by one substituent being oxo (=O), OH, NHR^{21}, C_{1-2}alkyl, C_{1-2}fluoroalkyl, $-CH_2OH$, $-C(O)OR^{23}$, $-C(O)NHR^{24}$, $-C(O)R^{25}$, fluoro, hydroxyimino (=N-OH), or (C_{1-4}alkoxy)imino (=N-OR^{26}); or cyclohexyl substituted by two fluoro substituents. More preferably, R^3 is cyclohexyl (i.e. unsubstituted); or cycloheptyl (i.e. unsubstituted); or cyclohexyl substituted by one substituent being oxo (=O), OH, NHR^{21}, C_{1-2}alkyl, C_{1-2}fluoroalkyl, $-C(O)OR^{23}$, $-C(O)NHR^{24}$, fluoro, hydroxyimino (=N-OH), or (C_{1-2}alkoxy)imino (=N-OR^{26} wherein R^{26} is C_{1-2}alkyl); or cyclohexyl substituted by two fluoro substituents. Still more preferably R^3 is cyclohexyl (i.e. unsubstituted) or cyclohexyl substituted by one oxo (=O), hydroxyimino (=N-OH), $-C(O)NH_2$, methyl or OH substituent. The optional substituent can for example be at the 3- or 4- position of the R^3 cyclohexyl ring. Preferably, any OH substituent is preferably at the 3-position of a R^3 cyclohexyl ring, and/or any oxo (=O), hydroxyimino (=N-OH), (C_{1-4}alkoxy)imino (=N-OR^{26}) or $-C(O)NH_2$ substituent is preferably at the 4-position of a R^3 cyclohexyl ring, and/or any alkyl or fluoroalkyl substituent is preferably at the 1-, 3- or 5- position of a R^3 cyclohexyl ring.

Alternatively, when R^3 is optionally substituted C_{3-8}cycloalkyl, R^3 can suitably be cyclobutyl optionally substituted with one substituent being oxo (=O); OH; NHR^{21} wherein R^{21} is a hydrogen atom (H); methyl; $-CH_2F$; $-CHF_2$; $-C(O)OR^{23}$; $-C(O)NHR^{24}$ wherein R^{24} is H or methyl (preferably H); fluoro; hydroxyimino (=N-OH); or methoxyimino (=N-OR^{26} where R^{26} is methyl). In this case, preferably R^3 is cyclobutyl optionally substituted by one $-C(O)NHR^{24}$ substituent wherein R^{24} is H or methyl (preferably H). R^3 can for example be cyclobutyl (i.e. unsubstituted) or

3-(aminocarbonyl)cyclobutyl (i.e. 3-(aminocarbonyl)cyclobutan-1-yl) (e.g. in a *cis* or *trans* configuration, preferably *cis*).

When R^3 is optionally substituted C_{6-7}cycloalkyl, R^3 can for example be 4-hydroxy-cyclohexyl (i.e. 4-hydroxycyclohexan-1-yl), 4-methylcyclohexyl, 2-aminocyclohexyl, or 3-oxocyclohexyl, but R^3 is more preferably cyclohexyl (i.e. unsubstituted), cycloheptyl (i.e. unsubstituted), 3-hydroxy-cyclohexyl (i.e. 3-hydroxycyclohexan-1-yl) (e.g. in a *cis* or *trans* configuration, preferably *cis*), 4-oxo-cyclohexyl (i.e. 4-oxocyclohexan-1-yl), 4-(hydroxyimino)cyclohexyl (i.e. 4-(hydroxyimino)cyclohexan-1-yl), 4-(C_{1-2}alkoxyimino)cyclohexyl, 4-(aminocarbonyl)cyclohexyl (i.e. 4-(aminocarbonyl)cyclohexan-1-yl) (e.g. in a *cis* or *trans* configuration, preferably *cis*), 1-methylcyclohexyl, 3-methylcyclohexyl, 4,4-(difluoro)cyclohexyl, or 3-aminocyclohexyl. Alternatively, R^3 can preferably be 4-acetylcyclohexyl (e.g. in a *cis* or *trans* configuration, preferably *cis*).

When R^3 is optionally substituted C_{6-7}cycloalkyl, R^3 is most preferably cyclohexyl (i.e. unsubstituted), 3-hydroxy-cyclohexyl (i.e. 3-hydroxycyclohexan-1-yl) (preferably in a *cis* configuration), 4-oxo-cyclohexyl (i.e. 4-oxocyclohexan-1-yl), 4-(hydroxyimino)cyclohexyl (i.e. 4-(hydroxyimino)cyclohexan-1-yl), or 4-(aminocarbonyl)cyclohexyl (i.e. 4-(aminocarbonyl)cyclohexan-1-yl) (preferably in a *cis* configuration).

When R^3 is optionally substituted C_5cycloalkyl (optionally substituted cyclopentyl), R^3 can for example be cyclopentyl (i.e. unsubstituted) or more suitably 3-hydroxy-cyclopentyl.

When R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, preferably it is optionally substituted mono-unsaturated-C_{5-6}cycloalkenyl, more preferably optionally substituted mono-unsaturated-C_6cycloalkenyl (i.e. optionally substituted mono-unsaturated-cyclohexenyl = optionally substituted cyclohexenyl). For example, the R^3 cyclohexenyl can be optionally substituted cyclohex-3-en-1-yl.

When R^3 is optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl, in one optional embodiment the R^3 cycloalkenyl is optionally substituted with one or two substituents independently being fluoro or methyl. Preferably, in this embodiment, if there are two substituents then they are not both methyl.

In another optional embodiment, the R^3 cycloalkenyl (e.g. cyclohexenyl) is optionally substituted with one substituent being fluoro or C_{1-2}alkyl (preferably fluoro or methyl); suitably the R^3 cycloalkenyl (e.g. cyclohexenyl) can be substituted with one fluoro

substituent or is unsubstituted. For example, the R^3 optionally substituted cycloalkenyl can be cyclohex-3-en-1-yl (i.e. unsubstituted) or 4-fluoro-cyclohex-3-en-1-yl.

For R^3 cycloalkenyl, the optional substituent(s) can for example be at the 1-, 2-, 3-, 4-, 5- or 6- position(s) of the cycloalkenyl ring.

When R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then Y is suitably O or NR^{10}. When R^3 is the heterocyclic group of sub-formula (aa) or (bb), then Y is preferably O or N-C(O)-NH_2.

Suitably, R^{10} is a hydrogen atom (H), methyl, ethyl, C(O)NH_2, C(O)-C_{1-2}alkyl or C(O)-C_1fluoroalkyl. Preferably, R^{10} is not C_{1-2}alkyl or C_{1-2}fluoroalkyl.

More preferably, R^{10} is a hydrogen atom (H), C(O)NH_2, C(O)-C_{1-2}alkyl (e.g. C(O)methyl) or C(O)-C_1fluoroalkyl (e.g. C(O)-CF_3). Still more preferably R^{10} is H, C(O)NH_2 or C(O)methyl; for example C(O)NH_2.

When R^3 is the heterocyclic group of sub-formula (aa), (bb) or (cc), then it is preferable that R^3 is the heterocyclic group of sub-formula (aa) or (bb), more preferably of sub-formula (bb).

In sub-formula (bb), n^1 is preferably 1. In sub-formula (cc), n^2 is preferably 1. That is, six-membered rings are preferred in the R^3 heterocyclic group.

Suitably, in R^3, the heterocyclic group of sub-formula (aa), (bb) or (cc) can be unsubstituted on a ring carbon. (In this connection, where Y is NR^{10}, R^{10} is not a substituent on a ring carbon).

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), the one or two optional substituents (i.e. the one or two optional ring-carbon substituents) preferably comprise (e.g. is or independently are) OH; oxo (=O); C_{1-2}alkyl (e.g. methyl) or C_{1-2}fluoroalkyl (e.g. C_1fluoroalkyl such as -CH_2F or -CHF_2). More preferably, in the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), the one or two optional substituents comprise (e.g. is or independently are) C_{1-2}alkyl (e.g. methyl) or oxo; most preferably the one or two optional substituents comprise (e.g. is or are) oxo (=O).

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any oxo (=O) substituent is preferably on a carbon atom bonded (adjacent) to Y, e.g. is on a carbon atom bonded (adjacent) to Y only when Y is O or NR^{10}.

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any oxo (=O) substituent can suitably be at the 2-, 3-, 4-, 5- or 6- position of the R^3 heterocyclic ring. For example any oxo (=O) substituent(s) can be: at the 2-, 4- or 5- position(s) (e.g. 2-position or 4-position, or two oxo substituents at 2- and 4- positions) of a R^3 heterocyclic group of sub-formula (aa), at the 2-, 4-, 5- or 6- position(s) (e.g. 4-position) of a six-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 1, at the 2-, 3-, 5-, 6- or 7-position(s) (e.g. 5-position) of a seven-membered R^3 heterocyclic group of sub-formula (bb) wherein n^1 is 2, or at the 2-, 4-, 5-, 6- or 7- position(s) (e.g. 2-position) of a seven-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 2.

(In this connection and generally herein, the 1-position of the R^3 heterocyclic ring is deemed to be the connection point to the -NH- in formula (I) = the ring atom connecting to the -NH- in formula (I), and the remaining positions of the ring are then numbered so that the ring heteroatom takes the lowest possible number).

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), any alkyl or fluoroalkyl substituent (ring-carbon substituent) can for example be at the 1-, 2-, 3-, 4-, 5- or 6-position, e.g. the 1-position, of the R^3 heterocyclic ring, for example at the 1-, 3- or 5-position of a six-membered R^3 heterocyclic ring.

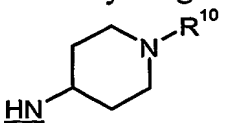
In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), then any OH substituent is: at the 5-position of a six-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 1; at the 5- or 6- position of a seven-membered R^3 heterocyclic group of sub-formula (cc) wherein n^2 is 2; or at the 6- position of a seven-membered R^3 heterocyclic group of sub-formula (bb) wherein n^1 is 2.

Any other optional ring-carbon substituents of the R^3 heterocyclic group can optionally be positioned on the R^3 heterocyclic ring at numerical positions as described herein for when R^3 is optionally substituted C_{5-7}cycloalkyl, all necessary changes to the wording being made.

In the R^3 heterocyclic group of sub-formula (aa), (bb) or (cc), preferably, only C_{1-2}alkyl, C_{1-2}fluoroalkyl, fluoro or oxo (=O) substitution or no substitution is allowed independently at each of the 2- and highest-numbered- positions of the R^3 heterocyclic ring (e.g. at each of the 2- and 6- positions of a six-membered R^3 heterocyclic ring), and/or only C_{1-2}alkyl, C_{1-2}fluoroalkyl or fluoro substitution or no substitution is allowed at the 1-position of the R^3 heterocyclic ring.

When R^3 is the heterocyclic group of sub-formula (aa) and Y is NR^{10}, then R^{10} is not C(O)-C_{1-2}alkyl, C(O)-C_1fluoroalkyl or -C(O)-CH_2O-C_1alkyl.

In one preferable embodiment, when R^3 is the heterocyclic group of sub-formula (aa) then Y is O, S, SO_2, NH or $NC(O)NH_2$ (e.g. O, S, SO_2 or NH).

When R^3 is the heterocyclic group of sub-formula (bb), n^1 is 1, and Y is NR^{10} (e.g. when NHR^3 is ), then R^{10} is not C_{1-2}alkyl or C_{1-2}fluoroalkyl. When R^3 is the heterocyclic group of sub-formula (bb) wherein n^1 is 1 or 2 and Y is NR^{10}, then preferably R^{10} is not C_{1-2}alkyl or C_{1-2}fluoroalkyl.

In one embodiment, when R^3 is the heterocyclic group of sub-formula (bb), then preferably Y is O, S, SO_2 or NR^{10} wherein R^{10} is H, $C(O)NH_2$, $C(O)$-C_{1-2}alkyl (e.g. C(O)methyl) or $C(O)$-C_1fluoroalkyl (e.g. $C(O)$-CF_3), or more preferably R^{10} is H, $C(O)NH_2$ or C(O)Me, for example $C(O)NH_2$ or C(O)Me, most preferably $C(O)NH_2$.

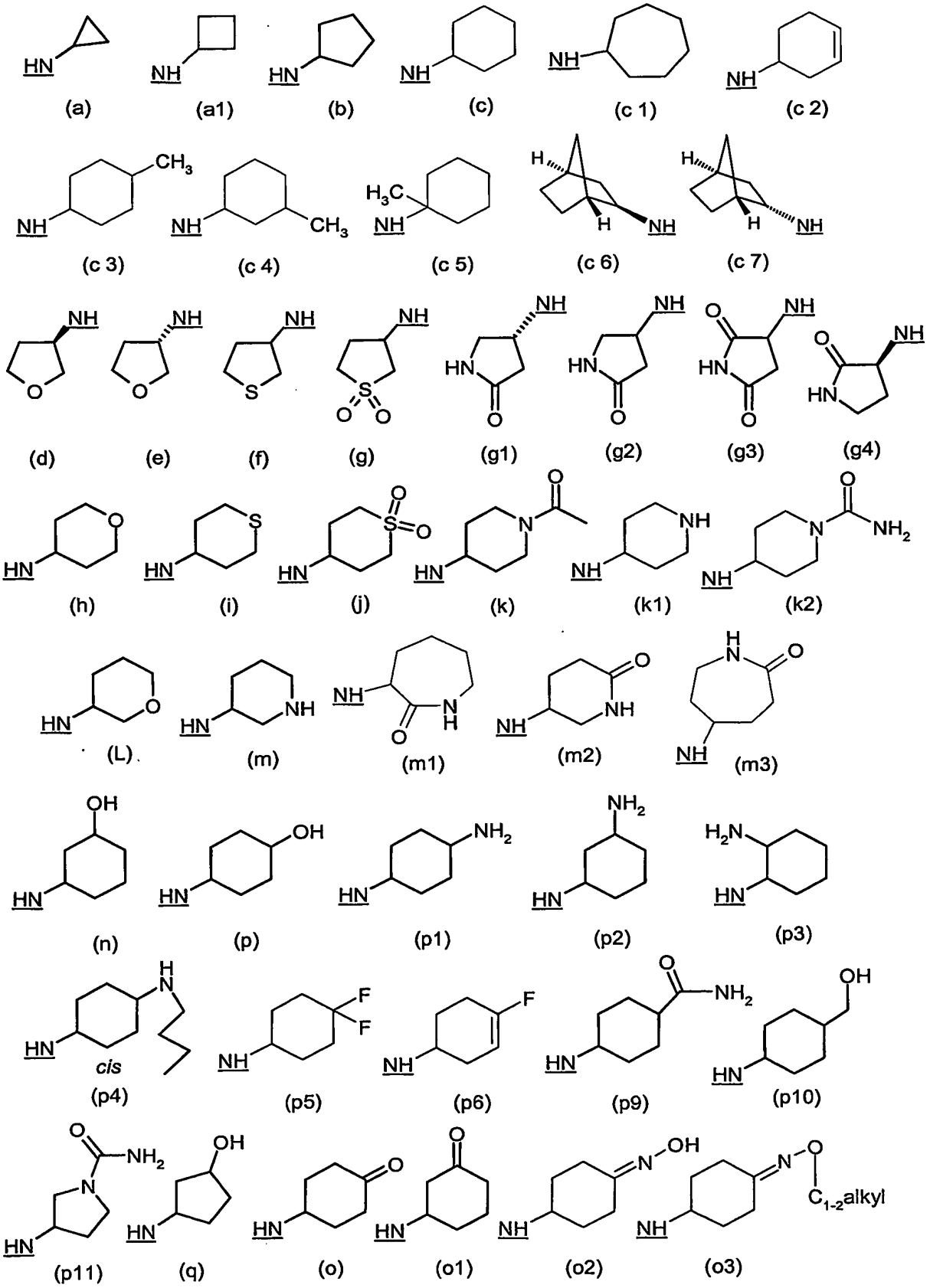
When R^3 is the heterocyclic group of sub-formula (cc), then Y is O, S, SO_2 or NR^{10} wherein R^{10} is H.

Optionally, for sub-formula (bb) and/or for sub-formula (cc), Y is O or NR^{10}.

When R^3 is optionally substituted C_{3-8}cycloalkyl (e.g. C_{6-7}cycloalkyl) or optionally substituted mono-unsaturated-C_{5-7}cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc), then a substituent can be in the *cis* or *trans* configuration with respect to the -NH- group of formula (I) to which R^3 is attached (bonded); this includes mixtures of configurations wherein the stated configuration is the major component. For example, an OH or $-C(O)NHR^{24}$ substituent on C_{6-7}cycloalkyl can for example be in the *cis* configuration and/or a NHR^{21} substituent on C_{6-7}cycloalkyl can for example be in the *cis* or *trans* configuration, with respect to the -NH- group of formula (I) to which R^3 is attached (bonded), including mixtures of configurations wherein the stated configuration is the major component.

When R^3 is a bicyclic group of sub-formula (ee), then preferably Y^1, Y^2 and Y^3 are all CH_2.

Preferably, NHR^3 is of sub-formula (a), (a1), (b), (c), (c 1), (c 2), (c 3), (c 4), (c 5), (c 6), (c 7), (d), (e), (f), (g), (g1), (g2), (g3), (g4), (h), (i), (j), (k), (k1), (k2), (L), (m), (m1), (m2), (m3), (n), (o), (o1), (o2), (o3), (p), (p1), (p2), (p3), (p4), (p5), (p6), (p9), (p10), (p11) or (q):


(a)
(a1)
(b)
(c)
(c 1)
(c 2)
(c 3)
(c 4)
(c 5)
(c 6)
(c 7)
(d)
(e)
(f)
(g)
(g1)
(g2)
(g3)
(g4)
(h)
(i)
(j)
(k)
(k1)
(k2)
(L)
(m)
(m1)
(m2)
(m3)
(n)
(p)
(p1)
(p2)
(p3)
cis
(p4)
(p5)
(p6)
(p9)
(p10)
(p11)
(q)
(o)
(o1)
(o2)
(o3)
C1-2alkyl

In the sub-formulae (a) to (q) etc above, the -NH- connection point of the NHR^3 group to the 4-position of the pyrazolopyridine of formula (I) is underlined.

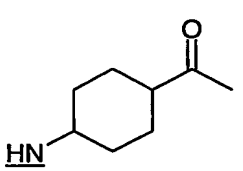
Preferably, NHR^3 is of sub-formula (c), (c1), (c 2), (c 3), (c 4), (c 5), (c 6), (c 7), (d), (e), (f), (g1), (g4), (h), (i), (j), (k), (k1), (k2), (L), (m), (m1), (m2), (m3), (n), (o), (o1), (o2), (o3), (p), (p2), (p5), (p6), (p9), (p10), (p11) or (q); or preferably NHR^3 is of sub-formula (a1), (c), (c1), (c 2), (c 3), (c 4), (c 5), (c 6), (c 7), (d), (e), (f), (g1), (g4), (h), (i), (j), (k), (k1), (k2), (L), (m), (m1), (m3), (n), (o), (o1), (o2), (o3), (p), (p1), (p2), (p5), (p6), (p9), (p10), (p11) or (q).

More preferably, NHR^3 is of sub-formula (c), (c1), (c 4), (c 5), (h), (i), (j), (k), (k2), (m1), (n), (o), (o2), (o3), (p2), (p5), (p6), (p9), (p11) or (q). NHR^3 can for example be of sub-formula (c), (h), (k), (k2), (n), (o), (o2), (p9) or (p11); or still more preferably (c), (h), (k2), (n), (o), (o2), (p9) or (p11). Most preferably, R^3 is tetrahydro-2H-pyran-4-yl or 1-(aminocarbonyl)-4-piperidinyl; that is NHR^3 is most preferably of sub-formula (h) or (k2), as shown above.

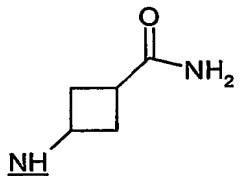
When NHR^3 is of sub-formula (n), then it can be in the *trans* configuration; but preferably it is in the *cis* configuration, i.e. preferably it is a *cis*-(3-hydroxycyclohexan-1-yl)amino group (including mixtures of configurations wherein the *cis* configuration is the major component), e.g. in any enantiomeric form or mixture of forms such as a racemic mixture.

When NHR^3 is of sub-formula (p9), then it can be in the *trans* configuration; but preferably it is in the *cis* configuration, i.e. preferably it is a *cis*-[4-(aminocarbonyl)cyclohexan-1-yl]amino group (including mixtures of configurations wherein the *cis* configuration is the major component).

In an alternative preferable embodiment, NHR^3 is of sub-formula (p12) or (p13):



(p12)



(p13)

In the sub-formulae (p12) and (p13) above, the -NH- connection point of the NHR^3 group to the 4-position of the pyrazolopyridine of formula (I) is underlined.

When NHR^3 is of sub-formula (p12) or (p13), then it can be in the *trans* configuration; but preferably it is in the *cis* configuration, i.e. preferably NHR^3 is a

cis-[4-acetylcyclohexan-1-yl]amino group or a *cis*-[3-(aminocarbonyl)cyclobutan-1-yl]amino group respectively (each including mixtures of configurations wherein the *cis* configuration is the major component).

Where R^4 is C_{1-2}fluoroalkyl, then it can be C_1fluoroalkyl such as monofluoromethyl, difluoromethyl or trifluoromethyl.

R^{4a} can suitably be a hydrogen atom (H) or methyl (Me), more suitably H.

R^4 can for example be a hydrogen atom (H); methyl, ethyl, C_1fluoroalkyl, $-CH_2OH$, $-CH(Me)OH$, $-CH_2CH_2OH$, or $-CH_2OMe$; or preferably a hydrogen atom (H), methyl, ethyl, CF_3, $-CH_2OH$, or $-CH_2OMe$. More preferably, R^4 is methyl, ethyl, CF_3, $-CH_2OH$, or $-CH_2OMe$; for example methyl, ethyl, CF_3 or $-CH_2OH$. Still more preferably, R^4 is methyl or ethyl. Most preferably, R^4 is ethyl.

Suitably, R^4 is not a hydrogen atom (H), and more suitably R^5 is a hydrogen atom (H).

When R^5 is C_{1-4}alkyl substituted by one substituent R^{11} or R^5 is C_{2-4}alkyl (e.g. ethyl or n-propyl) substituted on different carbon atoms by two OH substituents, then suitably R^5 is C_{1-4}alkyl substituted by one substituent R^{11}.

When R^5 is C_{1-4}alkyl substituted by one substituent R^{11}, it is suitable that R^5 is C_{1-3}alkyl (e.g. C_{1-2}alkyl) substituted by one substituent R^{11}. Suitably, R^5 is $-(CH_2)_{n^5}-R^{11}$ wherein n^5 is 1, 2, 3 or 4 or R^5 is $-CH(Me)-R^{11}$. Preferably n^5 is 1, 2 or 3, more preferably 1 or 2, still more preferably 1.

Suitably, R^{11} is: hydroxy (OH); C_{1-4}alkoxy or C_{1-2}alkoxy (such as t-butyloxy, ethoxy or preferably methoxy); C_1fluoroalkoxy; $-NR^{12}R^{13}$; $-NR^{15}-C(O)R^{16}$; or $-NR^{15}-S(O)_2R^{16}$. More suitably, R^{11} is hydroxy (OH), C_{1-4}alkoxy (e.g. C_{1-2}alkoxy), or $-NR^{12}R^{13}$; still more suitably OH, ethoxy, methoxy, NH_2, NHMe, NHEt, NMe_2, pyrrolidin-1-yl or piperidin-1-yl; preferably OH, methoxy, NH_2, NHMe or NMe_2.

Where R^5 is C_{1-8}alkyl, then suitably it is C_{1-6}alkyl or C_{1-5}alkyl or C_{1-4}alkyl or C_{1-3}alkyl. Where R^5 is C_{1-3}fluoroalkyl then suitably it is C_{1-2}fluoroalkyl or C_1fluoroalkyl such as monofluoromethyl, difluoromethyl or trifluoromethyl. Where R^5 is C_{3-8}cycloalkyl optionally substituted by a C_{1-2}alkyl group, then optionally the

C_{3-8}cycloalkyl is not substituted at the connecting ring-carbon. Where R^5 is optionally substituted C_{3-8}cycloalkyl, then suitably it is C_{3-8}cycloalkyl (i.e. unsubstituted) and/or optionally substituted C_{3-6}cycloalkyl such as optionally substituted cyclopropyl or optionally substituted cyclohexyl.

When R^5 is optionally substituted -$(CH_2)_n{}^4$-C_{3-8}cycloalkyl, then n^4 is preferably 1, and/or suitably R^5 is optionally substituted -$(CH_2)_n{}^4$-C_{3-6}cycloalkyl such as optionally substituted -$(CH_2)_n{}^4$-cyclopropyl or optionally substituted -$(CH_2)_n{}^4$-C_6cycloalkyl. When R^5 is optionally substituted -$(CH_2)_n{}^4$-C_{3-8}cycloalkyl, preferably it is not substituted. For example, R^5 can be (cyclohexyl)methyl-, that is -CH_2-cyclohexyl, or -CH_2-cyclopropyl.

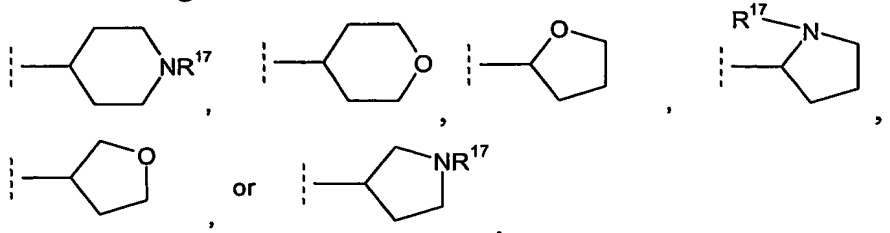
When R^{19} is C_{1-2}alkyl, then optionally it can be methyl.

When R^5 is -$(CH_2)_n{}^{11}$-C(O)R^{16}; -$(CH_2)_n{}^{11}$-C(O)$NR^{12}R^{13}$; -CHR^{19}-C(O)$NR^{12}R^{13}$; -$(CH_2)_n{}^{11}$-C(O)OR^{16}; -$(CH_2)_n{}^{11}$-C(O)OH; -CHR^{19}-C(O)OR^{16}; -CHR^{19}-C(O)OH; -$(CH_2)_n{}^{11}$-$S(O)_2$-$NR^{12}R^{13}$; -$(CH_2)_n{}^{11}$-$S(O)_2R^{16}$; or -$(CH_2)_n{}^{11}$-CN; then R^5 can suitably be -$(CH_2)_n{}^{11}$-C(O)$NR^{12}R^{13}$; -$(CH_2)_n{}^{11}$-C(O)OR^{16}; -$(CH_2)_n{}^{11}$-C(O)OH; or -$(CH_2)_n{}^{11}$-CN; or R^5 can more suitably be -$(CH_2)_n{}^{11}$-C(O)$NR^{12}R^{13}$; -$(CH_2)_n{}^{11}$-C(O)OR^{16} or -$(CH_2)_n{}^{11}$-CN; or preferably -$(CH_2)_n{}^{11}$-C(O)$NR^{12}R^{13}$ or -$(CH_2)_n{}^{11}$-C(O)OR^{16}.

Preferably, n^{11} is 0, 1 or 2. In one optional embodiment n^{11} is 0 or 1, for example 0. In a suitable embodiment, n^{11} is 2.

When R^5 is -$(CH_2)_n{}^{13}$-Het, n^{13} can for example be 0 or 1.

Suitably, Het is a 5- or 6-membered saturated or unsaturated heterocyclic ring, and/or preferably Het is a 4-, 5-, 6- or 7-membered saturated heterocyclic ring. Suitably, the heterocyclic ring Het contains one ring-hetero-atom selected from O, S and N. Suitably, the carbon ring-atoms in Het are not substituted. Het can for example be:



When R^5 is phenyl (Ph), $-CH_2$-Ph, -CHMe-Ph, -CHEt-Ph, CMe_2Ph, or $-CH_2CH_2$-Ph, wherein the phenyl ring Ph is optionally substituted, then suitably Ph is optionally substituted with one of the substituents defined herein. Preferably, R^5 is phenyl (Ph) or $-CH_2$-Ph wherein the phenyl ring Ph is optionally substituted with one or two substituents as defined herein.

When R^5 is phenyl (Ph), $-CH_2$-Ph, -CHMe-Ph, -CHEt-Ph, CMe_2Ph, or $-CH_2CH_2$-Ph, wherein the phenyl ring Ph is optionally substituted with one or two substituents, then preferably the phenyl ring Ph is optionally substituted with one or two (e.g. one) substituents independently being: fluoro; chloro; C_{1-2}alkyl (e.g. methyl); C_1fluoroalkyl (e.g. trifluoromethyl); C_{1-2}alkoxy (e.g. methoxy); or C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy). Ph can be unsubstituted.

When R^4 and R^5 taken together are $-(CH_2)_p{}^1-$ or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$, in which X^5 is O or NR^{17a}; then preferably R^4 and R^5 taken together are $-(CH_2)_p{}^1-$. In one embodiment of the invention, R^4 and R^5 are not taken together to be either $-(CH_2)_p{}^1-$ or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$.

When R^4 and R^5 taken together are $-(CH_2)_p{}^1-$, then p^1 can for example be 2, 4, 5 or 6. p^1 is preferably 2, 4 or 5, more preferably 2 or 4.

When R^4 and R^5 taken together are $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$, in which X^5 is O or NR^{17a}; then suitably: p^3 is 2, and/or p^4 is 2, and/or one of p^3 and p^4 is 1 and the other of p^3 and p^4 is 2, and/or p^3 and p^4 are both 1. Suitably, X^5 is O. $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$ can for example be $-(CH_2)_2-O-(CH_2)_2-$.

In one embodiment of the invention, R^4 and R^5 are not taken together as $-(CH_2)_p{}^1-$ or $-(CH_2)_p{}^3-X^5-(CH_2)_p{}^4-$.

It is preferable that Ar has the sub-formula (x).

Preferably, in sub-formula (x), two or more (more preferably three or more) of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine) or nitrogen (N).

Suitably, in sub-formula (x), three or more of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), nitrogen (N), or nitrogen-oxide (N^+-O^-).

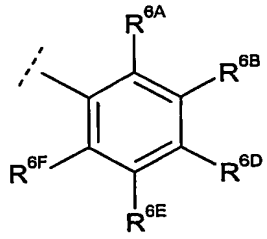
Preferably, in sub-formula (x), two or more (e.g. three or more) of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), or nitrogen (N); and one or more (e.g. two or more) others of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), C-Cl (carbon-chlorine), C-Me, C-OMe, or nitrogen (N). More preferably, in sub-formula (x), two or more (e.g. three or more) of A, B, D, E and F are C-H (carbon-hydrogen); and one or more (e.g. two or more) others of A, B, D, E and F are independently C-H (carbon-hydrogen), C-F (carbon-fluorine), C-Cl (carbon-chlorine), C-Me, C-OMe, or nitrogen (N).

Preferably, in sub-formula (x), two or more (e.g. three or more, e.g. four or more) of A, B, D, E and F are C-H.

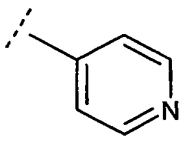
Preferably, in sub-formula (x), no more than one (more preferably none) of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-).

Preferably, in sub-formula (x), none of A, B, D, E and F are nitrogen-oxide (N^+-O^-).

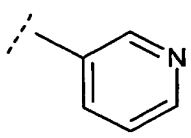
Preferably, Ar has the sub-formula (x) which is sub-formula (x1), (x2), (x3), (x4), (x5), (x6), (x7), (x8), (x9), (x10), (x11), (x12), (x12a), (x13), (x14), (x15) or (x16):



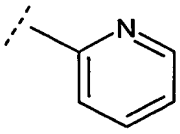
(x1)



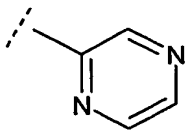
(x2)



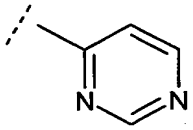
(x3)



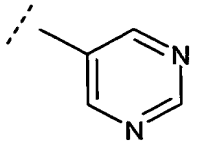
(x4)



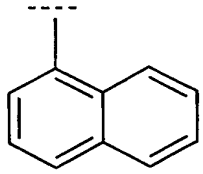
(x5)



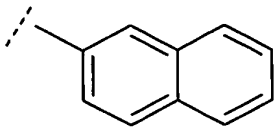
(x6)



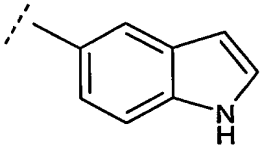
(x7)



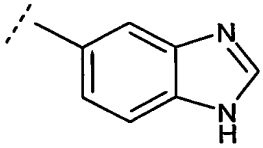
(x8)



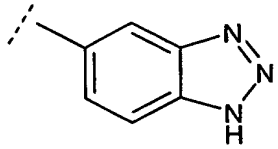
(x9)



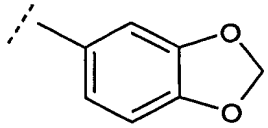
(x10)



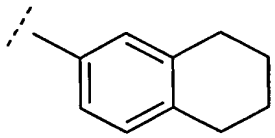
(x11)



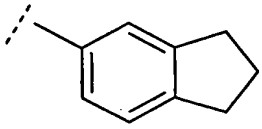
(x12)



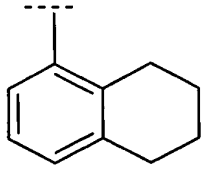
(x12a)



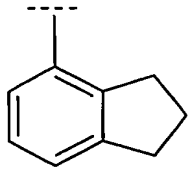
(x13)



(x14)



(x15)



(x16)

In one preferable embodiment, Ar has the sub-formula (x) which is sub-formula (x1), (x2), (x3), (x4), (x5), (x6), (x7), (x8), (x9), (x10), (x11), (x12), (x13), (x14), (x15) or (x16).

More preferably, Ar has the sub-formula (x) which is sub-formula (x1), (x2), (x3), (x8), (x13), or (x14). Still more preferably, Ar has the sub-formula (x) which is sub-formula (x1), (x8), (x13), or (x14). Most preferably, Ar has the sub-formula (x) which is sub-formula (x1).

In sub-formula (x), preferably, R^{6A}, R^{6B}, R^{6D}, R^{6E} and/or R^{6F}, independently of each other, is or are: a hydrogen atom (H), a fluorine, chlorine, bromine or iodine atom, methyl, ethyl, n-propyl, isopropyl, C_4alkyl, trifluoromethyl, -CH_2OH, methoxy, ethoxy, n-propoxy, isopropoxy, C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy), cyclohexyloxy; cyclopentyloxy; nitro (-NO_2), OH, C_{1-3}alkylS(O)$_2$- (such as MeS(O)$_2$-),

C_{1-3}alkylS(O)$_2$-NH- such as Me-S(O)$_2$-NH-, Me_2N-S(O)$_2$-, H_2N-S(O)$_2$-, -$CONH_2$, -CONHMe, -C(O)OH, cyano (-CN), NMe_2, or C_{1-2}alkyl-S(O)$_2$-CH_2- such as Me-S(O)$_2$-CH_2-.

More preferably, R^{6A}, R^{6B}, R^{6D}, R^{6E} and/or R^{6F}, independently of each other, is or are: a hydrogen atom (H), a fluorine, chlorine, bromine or iodine atom, methyl, ethyl, n-propyl, isopropyl, isobutyl, trifluoromethyl, -CH_2OH, methoxy, ethoxy, n-propoxy, isopropoxy, C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy), nitro (-NO_2), OH, C_{1-3}alkylS(O)$_2$- such as MeS(O)$_2$-, C_{1-2}alkylS(O)$_2$-NH- such as Me-S(O)$_2$-NH-, -$CONH_2$, cyano (-CN), or C_{1-2}alkylS(O)$_2$-CH_2- such as Me-S(O)$_2$-CH_2.

Still more preferably, R^{6A}, R^{6B}, R^{6D}, R^{6E} and/or R^{6F}, independently of each other, is or are: a hydrogen atom (H), a fluorine, chlorine or bromine atom, methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, -CH_2OH, methoxy, ethoxy, n-propoxy, difluoromethoxy, OH or MeS(O)$_2$-.

When two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are taken together, then, preferably, when taken together they are: –CH=CH–CH=CH–, –$(CH_2)_n{}^{14a}$– where n^{14a} is 3, 4 or 5 (e.g. 3 or 4), –O–(CMe_2)–O–, –O–$(CH_2)_n{}^{14b}$–O– where n^{14b} is 1 or 2; -CH=CH-NR^{15b}-; -N=CH-NR^{15b}-; -N=N-NR^{15b} wherein R^{15b} is H or C_{1-2}alkyl (preferably R^{15b} is H). More preferably, in this embodiment, two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are taken together and are: –CH=CH–CH=CH_2– or –$(CH_2)_n{}^{14a}$– where n^{14a} is 3, 4 or 5 (e.g. 3 or 4).

In sub-formula (x), e.g. in sub-formula (x1), suitably, one, two or three of R^{6B}, R^{6D} and R^{6E} are other than a hydrogen atom (H).

In sub-formula (x), e.g. in sub-formula (x1), suitably, one or both of R^{6A} and R^{6F} are independently a hydrogen atom (H), a fluorine atom (F), or methyl. For example, one or both of R^{6A} and R^{6F} can be a hydrogen atom (H).

In sub-formula (x), e.g. in sub-formula (x1), suitably the ring or ring system is unsubstituted, monosubstituted, disubstituted or trisubstituted; or preferably the ring or ring system is unsubstituted, monosubstituted or disubstituted; more preferably monosubstituted or disubstituted. In sub-formula (x), e.g. in sub-formula (x1), for monosubstitution of the ring or ring system, then the one substituent selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} is suitably present at the 3- or 4-position with respect to the –(CR^4R^5)– side-chain (i.e., for a 4-position substituent, D is CR^{6D} where R^{6D} is other than H), or is a 2-methyl, 2-ethyl, 2-fluoro or 2-chloro substituent. In sub-formula (x), e.g. in sub-formula (x1), for disubstitution of the ring or ring system, then 3,4-

disubstitution, 2,4-disubstitution, 2,3-disubstitution or 3,5-disubstitution is suitable. In sub-formula (x), 2,5-disubstitution is also suitable.

In one preferable embodiment, Ar has the sub-formula (x1) and is: phenyl, monoalkyl-phenyl-, mono(fluoroalkyl)-phenyl-, monohalo-phenyl-, monoalkoxy-phenyl-, mono(fluoroalkoxy)-phenyl-, mono(N,N-dimethylamino)-phenyl-, mono(methyl-SO_2-NH-)-phenyl-, mono(methyl-SO_2-)-phenyl-, dialkyl-phenyl-, monoalkyl-monohalo-phenyl-, mono(fluoroalkyl)-monohalo-phenyl-, dihalo-phenyl-, dihalo-monoalkyl-phenyl-, dihalo-mono(hydroxymethyl)-phenyl- (e.g. 2,3-dichloro-6-(hydroxymethyl)-phenyl-), or dialkoxy-phenyl- such as 3,4-dimethoxy-phenyl-. The substituents can preferably be further defined, as defined in preferable embodiments herein.

In one preferable embodiment, Ar is of sub-formula (x1) and is: monoalkyl-phenyl-, mono(fluoroalkyl)-phenyl-, monohalo-phenyl-, monoalkoxy-phenyl-, mono(fluoroalkoxy)-phenyl-, dialkyl-phenyl-, monoalkyl-monohalo-phenyl-, dihalo-phenyl- or dihalo-monoalkyl-phenyl-.

More preferably, in this embodiment, Ar is:
- monoC_{1-4}alkyl-phenyl- or monoC_{1-3}alkyl-phenyl- such as 4-C_{1-4}alkyl-phenyl- (e.g. 4-C_{1-3}alkyl-phenyl-) or 2-C_{1-2}alkyl-phenyl-;
- monoC_1fluoroalkyl-phenyl- such as 4-C_1fluoroalkyl-phenyl-;
- monoC_{1-3}alkoxy-phenyl- such as 4-C_{1-3}alkoxy-phenyl- or 3-C_{1-3}alkoxy-phenyl-;
- mono(C_1fluoroalkoxy)-phenyl- such as 4-C_1fluoroalkoxy-phenyl-;
- diC_{1-3}alkyl-phenyl- or diC_{1-2}alkyl-phenyl- or dimethyl-phenyl- such as 3,4-dimethyl-phenyl-, 2,4-dimethyl-phenyl-, 3,5-dimethyl-phenyl-, 2,3-dimethyl-phenyl- or 2,5-dimethyl-phenyl-; for example 3,4-dimethyl-phenyl-, 2,4-dimethyl-phenyl-, 2,3-dimethyl-phenyl- or 3,5-dimethyl-phenyl-;
- monoC_{1-3}alkyl-monohalo-phenyl-, such as monoC_{1-2}alkyl-monohalo-phenyl- and/or monoC_{1-3}alkyl-monochloro-phenyl- or monoC_{1-3}alkyl-monofluoro-phenyl-, for example 4-methyl-3-chloro-phenyl-, 3-methyl-4-chloro-phenyl-, or 2-methyl-4-chloro-phenyl-;
- dihalo-phenyl- such as 2-chloro-4-fluorophenyl- or 2,4-difluoro-phenyl- or 4-bromo-2-fluorophenyl- or preferably 4-chloro-2-fluorophenyl-; for example dichloro-phenyl- such as 3,4-dichloro-phenyl- or 2,4-dichloro-phenyl- or 2,6-dichloro-phenyl- or preferably 2,3-dichloro-phenyl-; or
- dihalo-monoC_{1-2}alkyl-phenyl- e.g. 2,4-dichloro-6-methyl-phenyl-.

In an alternative preferable embodiment, Ar has the sub-formula (x1) and is triC_{1-2}alkyl-phenyl- such as trimethylphenyl-, e.g. 2,4,6-trimethylphenyl-.

In an alternative embodiment, Ar has the sub-formula (z).

Preferably, in sub-formula (z), three or more (for example all) of J, L, M and Q are independently C-H, C-F, C-C_{1-2}alkyl (e.g. C-Me), C-[connection point to formula (I)], or nitrogen (N).

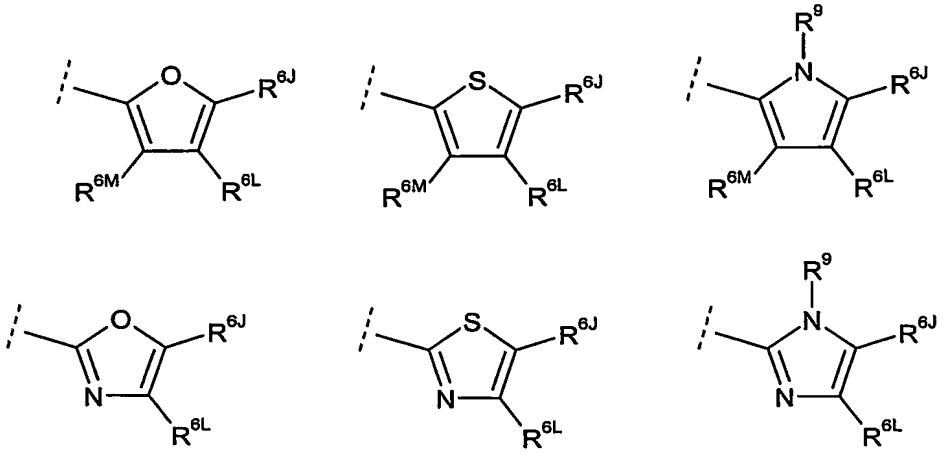
Preferably, in sub-formula (z), no more than two (for example no more than one) of J, L, M and Q are nitrogen (N).

Suitably, Q is C-[connection point to formula (I)].

Suitably, R^9 is a hydrogen atom (H) or methyl.

Suitably, R^{6J}, R^{6L}, R^{6M} and/or R^{6Q} independently is or are: a hydrogen atom (H); fluoro; chloro; C_{1-2}alkyl (e.g. methyl); C_1fluoroalkyl (e.g. CF_3); C_{1-2}alkoxy (methoxy); C_1fluoroalkoxy (e.g. CF_2HO-); OH (including any tautomer thereof); or phenyl optionally substituted by one substituent being fluoro, methyl, C_1fluoroalkyl, methoxy or C_1fluoroalkoxy. More suitably, R^{6J}, R^{6L}, R^{6M} and/or R^{6Q} independently is or are H, OH (including any keto tautomer thereof), or more preferably C_{1-2}alkyl (e.g. methyl) or C_1fluoroalkyl.

When Ar has the sub-formula (z), then sub-formula (z) can suitably be one of the following:



Suitably, R^{7a} is H or C_{1-2}alkyl, more suitably H or methyl. Suitably, R^{8a} is H.

Preferably, R^7 and/or R^8 are independently a hydrogen atom (H); C_{1-2}alkyl such as methyl; C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two (e.g. one) substituents independently being: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or

C_1fluoroalkoxy; or R^7 and R^8 together are $-(CH_2)_n{}^6-$ or $-(CH_2)_n{}^8-X^7-(CH_2)_n{}^9-$ wherein X^7 is NR^{14} or preferably O.

When R^7 is cycloalkyl or optionally substituted phenyl, then preferably R^8 is neither cycloalkyl nor optionally substituted phenyl. In this case, R^8 can for example be H.

More preferably, R^7 and/or R^8 independently are a hydrogen atom (H) or C_{1-2}alkyl. It is preferable that R^8 is a hydrogen atom (H).

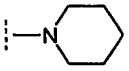
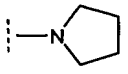
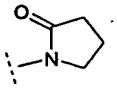
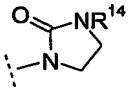
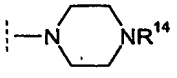
Preferably n^6 is 4 or 5. Preferably n^7 is 3 or 4. Preferably, n^8, n^9 and/or n^{10} independently is/are 2.

Preferably, R^{12} and/or R^{13} independently are H; C_{1-2}alkyl such as methyl; C_{3-6}cycloalkyl; or phenyl optionally substituted by one or two (e.g. one) substituents independently being: fluoro, chloro, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or R^{12} and R^{13} together are $-(CH_2)_n{}^{6a}-$ or $-(CH_2)_n{}^{8a}-X^{12}-(CH_2)_n{}^{9a}-$ in which X^{12} is NR^{14a} or preferably O.

When R^{12} is cycloalkyl or optionally substituted phenyl, then preferably R^{13} is neither cycloalkyl nor optionally substituted phenyl. In this case, R^{13} can for example be H.

More preferably, R^{12} and/or R^{13} independently are a hydrogen atom (H) or C_{1-2}alkyl. It is preferable that R^{13} is a hydrogen atom (H).

Preferably n^{6a} is 4 or 5. Preferably n^{7a} is 3 or 4. Preferably, n^{8a}, n^{9a} and/or n^{10a} independently is/are 2.

In one embodiment of the invention, NR^7R^8 and/or $NR^{12}R^{13}$ can for example independently be  , or  , or  , or  , or  (i.e. R^{12} and R^{13} together are $-(CH_2)_2-N(R^{14})-(CH_2)_2-$, or R^7 and R^8 together are $-(CH_2)_2-N(R^{14a})-(CH_2)_2-$ respectively), or  (i.e. R^{12} and R^{13} together or R^7 and R^8 together are $-(CH_2)_2-O-(CH_2)_2-$), or NMe_2.

Suitably, R^{14}, R^{14a}, R^{17} and/or R^{17a} independently are: a hydrogen atom (H); C_{1-2}alkyl; C_1fluoroalkyl (e.g. CF_3); -C(O)Me; $-C(O)NH_2$; or $-S(O)_2Me$. More suitably,

R^{14}, R^{14a}, R^{17} and/or R^{17a} independently is/are: H, C_{1-2}alkyl, or -C(O)Me; or for example H or C_{1-2}alkyl.

Suitably, R^{15} is a hydrogen atom (H) or C_{1-4}alkyl (e.g. ^{t}Bu or C_{1-2}alkyl e.g. methyl); more suitably, R^{15} is a hydrogen atom (H).

Where R^{15a}, independent of other R^{15a}, is a hydrogen atom (H) or C_{1-4}alkyl, it can for example be H, ^{t}Bu or C_{1-2}alkyl such as methyl. Suitably, R^{15a}, independent of other R^{15a}, is H or C_{1-2}alkyl, more preferably H.

Preferably, R^{15b} is H.

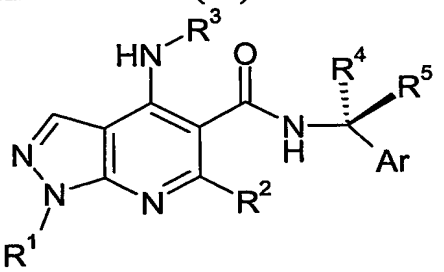
Suitably, R^{16} is C_{1-4}alkyl (e.g. C_{1-2}alkyl) or C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl); more suitably R^{16} is C_{1-4}alkyl (e.g. C_{1-2}alkyl).

Suitably, R^{16a} is:
C_{1-4}alkyl (e.g. C_{1-2}alkyl);
C_{3-6}cycloalkyl (e.g. C_{5-6}cycloalkyl) optionally substituted by one oxo (=O), OH or methyl substituent (e.g. optionally substituted at the 3- or 4-position of a C_{5-6}cycloalkyl ring; and/or preferably unsubstituted C_{3-6}cycloalkyl);
C_{3-6}cycloalkyl-CH_2- (e.g. C_{5-6}cycloalkyl-CH_2-);
pyridinyl (e.g. pyridin-2-yl) optionally substituted on a ring carbon atom by one of: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;
Ar^{5c};
phenyl optionally substituted by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy;
benzyl optionally substituted on its ring by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or
a 5- or 6-membered saturated heterocyclic ring connected at a ring-carbon and containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-nitrogens which are present are present as NR^{27} where R^{27} is H, C_{1-2}alkyl or -C(O)Me (preferably H or C_{1-2}alkyl); and wherein the ring is not substituted at carbon.

Preferably, R^{16a} is: C_{1-4}alkyl (e.g. C_{1-2}alkyl); unsubstituted C_{3-6}cycloalkyl (e.g. unsubstituted C_{5-6}cycloalkyl); phenyl optionally substituted by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy; or benzyl optionally substituted on its ring by one or two substituents independently being: a halogen atom, C_{1-2}alkyl, C_1fluoroalkyl, C_{1-2}alkoxy or C_1fluoroalkoxy. Preferably, R^{16a} is C_{1-4}alkyl (e.g. C_{1-2}alkyl).

Suitably, R^{30}, independent of other R^{30}, is a hydrogen atom (H) or C_{1-4}alkyl, for example H, t-butyl or C_{1-2}alkyl.

Preferably, the compound of formula (I) or the salt thereof is racemic at the carbon atom bearing the R^4 and R^5 groups, or (more preferably) the compound of formula (I) or the salt thereof is a compound of formula (IA) or a salt thereof:



(IA)

Formula (IA) means that more than 50% of the compound or salt present has the stereochemistry shown at the carbon atom bearing the R^4 and R^5 groups.

In Formula (IA), on a molarity basis, preferably 70% or more, more preferably 75% or more, still more preferably 85% or more, yet more preferably 90% or more, for example 95% or more such as 98% or more, of the compound or salt present has the stereochemistry shown at the carbon atom bearing the R^4 and R^5 groups.

Preferably, in Formula (IA), the stereochemistry at the carbon atom bearing the R^4 and R^5 groups is such that there is an enantiomeric excess (e.e.) of 50% or more at the carbon atom bearing the R^4 and R^5 groups (ignoring the stereochemistry at any other carbon atoms). More preferably, the enantiomeric excess (e.e.) is 70% or more or 80% or more, still more preferably 90% or more, yet more preferably 95% or more, at the carbon atom bearing the R^4 and R^5 groups (ignoring the stereochemistry at any other carbon atoms).

"Enantiomeric excess" (e.e.) is defined as the percentage of the major isomer present minus the percentage of the minor isomer present. For example, if 95% of major isomer is present and 5% of the minor isomer is present, then the e.e. would be 90%.

In formula (IA), it is preferable that R^4 is not a hydrogen atom (H). In formula (IA), more preferably R^4 is methyl, ethyl, C_1fluoroalkyl (such as CF_3), $-CH_2OH$, or $-CH_2OMe$; still more preferably R^4 is methyl, ethyl, CF_3 or $-CH_2OH$; yet more preferably R^4 is methyl or ethyl; and most preferably R^4 is ethyl.

In formula (IA), it is particularly preferable that R^5 is a hydrogen atom (H) and R^4 is not a hydrogen atom (H). In formula (IA), it is more preferable that R^5 is a hydrogen atom (H); and R^4 is methyl, ethyl, C_1 fluoroalkyl (such as CF_3), $-CH_2OH$, or $-CH_2OMe$ (e.g. methyl, ethyl, CF_3 or $-CH_2OH$). In formula (IA), it is most preferable that R^5 is a hydrogen atom (H); and R^4 is methyl or ethyl (preferably ethyl).

In formula (IA), when R^4 is not a hydrogen atom (H), and optionally when R^5 is a hydrogen atom (H), it is particularly preferable that Ar, such as having sub-formula (x1), is a monocycle. That is, in formula (IA) and when R^4 is not a hydrogen atom (H), it is particularly preferable that two adjacent groups selected from R^{6A}, R^{6B}, R^{6D}, R^{6E} and R^{6F} are not taken together to form part of a second ring.

The Examples 1, 8, 24, 28, 63, 127, 129, 174, and 178 disclosed herein, having and/or believed to have the formula (IA) wherein R^5 is H, and wherein R^4 is methyl, ethyl, $-CH_2OH$, or $-CH_2OMe$, and wherein Ar is a monocycle, generally have greater PDE4B inhibitory activity than the comparable Examples 6, 7, 29, 26, 64, 126, 124, 170, and 177 which have and/or are believed to have the opposite stereochemistry (including a majority of the opposite stereochemistry) at the CR^4R^5 (benzylic) carbon atom.

In an especially preferable embodiment, HN-CR^4R^5-Ar is the HN-CR^4R^5-Ar group as defined in any one of Examples 1 to 314 and/or as defined in any one of Examples 315 to 382.

It is particularly preferred that the compound of formula (I) or the salt thereof is:

1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-methyl-1-phenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-(diphenylmethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(3-pyridinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*S*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-methyl-1-(4-pyridinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(3-hydroxy-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[2-(dimethylamino)-1-phenylethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-phenyl-2-(1-pyrrolidinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(hydroxymethyl)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(propyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
methyl 3-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-phenylpropanoate
1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
ethyl ({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)(phenyl)acetate
1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*)-2-(methyloxy)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[(1*R*)-2-amino-2-oxo-1-phenylethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-2-(methyloxy)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(2-hydroxy-1,1-diphenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3-cyanophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[cyano(phenyl)methyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{cyclopropyl[4-(methyloxy)phenyl]methyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-(1,2-diphenylethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(methyloxy)phenyl]butyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*)-1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(aminocarbonyl)-1-phenylpropyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-phenylcyclopentyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(4-phenyltetrahydro-2*H*-pyran-4-yl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-phenylcyclopropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[4-(cyclohexyloxy)-3-methylphenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[3-(cyclohexyloxy)-4-(methyloxy)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[4-(cyclohexyloxy)-3-hydroxyphenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[4-(cyclopentyloxy)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-{1-[4-(1,1-dimethylethyl)phenyl]cycloheptyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-bromophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*)-1-(4-iodophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[4-(aminosulfonyl)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-methyl-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(1,3-benzodioxol-5-yl)cyclohexyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(methyloxy)phenyl]cyclohexyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)cyclohexyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3-chlorophenyl)cyclopentyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2-chlorophenyl)cyclopentyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-{1-[4-(1,1-dimethylethyl)phenyl]cyclohexyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{(1*S*)-1-[4-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-phenylhexyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-phenylpentyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(2-methyl-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-phenylbutyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-(2,2,2-trifluoro-1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[cyclopropyl(phenyl)methyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-phenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,4-dichlorophenyl)-2-hydroxyethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-bromophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(propyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-methylphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(2-methylphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-bromophenyl)-2,2,2-trifluoroethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{2,2,2-trifluoro-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-(diphenylmethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
ethyl ({[4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)(phenyl)acetate
N-[1-(4-chlorophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-(1-methyl-1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-(1,2-diphenylethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
methyl 3-({[4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-phenylpropanoate
4-(cyclohexylamino)-1-ethyl-*N*-[1-(hydroxymethyl)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-(3-hydroxy-1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-phenyl-2-(1-pyrrolidinyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[2-(dimethylamino)-1-phenylethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-2-(methyloxy)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[(1*R*)-2-amino-2-oxo-1-phenylethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-2-(methyloxy)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-1-(1-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[phenyl(4-phenyl-1,3-thiazol-2-yl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[cyano(phenyl)methyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(1-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-(2-hydroxy-1,1-diphenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[(1*R*)-1-(4-bromophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-bromophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(2-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chloro-2-fluorophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3-chloro-4-methylphenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chloro-2-fluorophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3-chloro-4-methylphenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)-2-hydroxyethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-*N*-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-(cyclohexylamino)-1-ethyl-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*S*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*R*)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-[(1-acetyl-4-piperidinyl)amino]-*N*-(diphenylmethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*)-1-(4-nitrophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-(1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
(2*R*)-[({1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl}carbonyl)amino][3-(methyloxy)phenyl]ethanoic acid
1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(2-methylphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-bromophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-methylphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-bromophenyl)-2,2,2-trifluoroethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{2,2,2-trifluoro-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[3-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-bromophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(4-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(2-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(2-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

N-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(3-hydroxyphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(3-hydroxyphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Isomer 1)
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Isomer 2)
N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)propyl]-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)ethyl]-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
N-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
N-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
N-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
N-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
N-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)
N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)
1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Diastereoisomer 1)
1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Diastereoisomer 2)
N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2) hydrochloride
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide, or
4-{[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide (for example, 4-{*cis*-[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide);

as a compound **or** a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

The structures of the above-listed specific compounds, or embodiments thereof, are given in Examples 1 to 314A hereinafter.

It is particularly preferred that the compound of formula (I) or the salt thereof is one of Examples 1 to 314 or Example 314A, as a compound or a salt thereof, e.g. a pharmaceutically acceptable salt thereof. The structures of these specific compounds, or embodiments thereof, are given in Examples 1 to 314 hereinafter, and their names are given in the Examples section.

In one embodiment, is still further preferred that the compound of formula (I) or the salt thereof is a compound of Example 73, 98, 283, 304, 306, 307, 310 or 311 (or is a compound of Example 75), as defined by the structures and/or names described herein, or a salt thereof, e.g. a pharmaceutically acceptable salt thereof. The structures and names of these Examples are described in the Examples section. These Examples can for example be for inhaled administration e.g. to a mammal such as a human, and/or can be contained in a pharmaceutical composition suitable and/or adapted for inhaled administration, and/or can be in a particle-size-reduced form (e.g. in a size-reduced form obtained or obtainable by micronisation, e.g. see "Particle size reduction" section below).

In an alternative preferable embodiment, the compound of formula (I) or the salt thereof is:

N-[(1S)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(1R)-1-(2,5-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-N-[(1R)-1-(2,4,6-trimethylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
1-ethyl-N-[(1R)-1-(2-ethylphenyl)ethyl]-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
1-ethyl-N-[(1R)-1-(4-ethylphenyl)ethyl]-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
1-ethyl-N-[(1R)-1-(4-methylphenyl)propyl]-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
1-ethyl-N-[(1R)-1-(4-ethylphenyl)propyl]-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
1-ethyl-N-{(1R)-1-[4-(1-methylethyl)phenyl]propyl}-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(1R)-1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(1R)-1-(2,6-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(1R)-1-(2,5-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
1-ethyl-N-[(1R)-1-(2-ethylphenyl)propyl]-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-N-[(1R)-1-(2,4,6-trimethylphenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(2,5-dimethylphenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-ethylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(2-ethylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(2,4,6-trimethylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(4-chlorophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-phenylpropyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(4-chlorophenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[1-(4-fluorophenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-ethylphenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-{(1R)-1-[4-(1-methylethyl)phenyl]propyl}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(2,6-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(2,5-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(2-ethylphenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(2,4,6-trimethylphenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[4-(aminocarbonyl)cyclohexyl]amino}-N-[1-(4-chlorophenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylpropyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[4-(aminocarbonyl)cyclohexyl]amino}-N-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[4-(aminocarbonyl)cyclohexyl]amino}-N-[1-(4-chlorophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

4-{[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[1-(4-fluorophenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[4-(aminocarbonyl)cyclohexyl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[(3S)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[(3S)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[(3S)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[(3S)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[(3R)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[(3R)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[(3R)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[(3R)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[*cis*-3-(aminocarbonyl)cyclobutyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[*cis*-3-(aminocarbonyl)cyclobutyl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-[(*trans*-4-acetylcyclohexyl)amino]-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

4-[(4-acetylcyclohexyl)amino]-N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-[(*cis*-4-acetylcyclohexyl)amino]-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
1-ethyl-4-{[*trans*-3-hydroxycyclohexyl]amino}-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(1S)-1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[*trans*-3-hydroxycyclohexyl]amino}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(1R)-1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[*trans*-3-hydroxycyclohexyl]amino}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-4-{[*trans*-3-hydroxycyclohexyl]amino}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-{[*trans*-3-hydroxycyclohexyl]amino}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
N-[4-(dimethylamino)-1-(3-methylphenyl)-4-oxobutyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[4-(dimethylamino)-1-(3-methylphenyl)-4-oxobutyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-4-(4-piperidinylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide hydrochloride, or
N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(4-piperidinylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide hydrochloride;

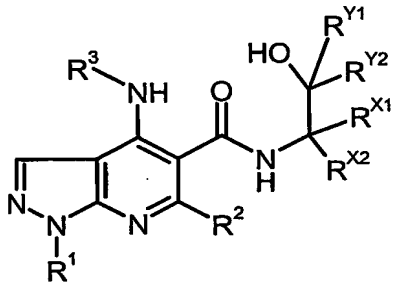
as a compound **or** a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

The structures of the above specific compounds, or embodiments thereof, are given in Examples 315 to 372 and Examples 374 to 382 hereinafter, and their names are given in the Examples section.

In a preferred embodiment of the above list of compounds (Examples 315 to 372 and Examples 374 to 382), it is further preferred that the compound of formula (I) or the salt thereof is a compound of Example 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 341, 342, 343, 344, 345, 351, 352, or 353, as defined by the structures and/or names described herein, or a salt thereof, e.g. a pharmaceutically acceptable salt thereof. Of these, Examples 316-333, 335, 338-345, and 351-353, are believed to consist essentially of an enantiomer which is believed to have the (R)-stereochemistry at the benzylic carbon atom. It is still further preferred that the compound of formula (I) or the salt thereof is a compound of Example 316, 321, 324, 326, 327, 328, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 343, 344 or 345, as defined by the structures and/or names described herein, or a salt thereof, e.g. a pharmaceutically acceptable salt thereof. The structures and names of these Examples are described in the Examples section.

In a preferred embodiment of the above list of compounds (Examples 315 to 372 and Examples 374 to 382), is yet further preferred that the compound of formula (I) or the salt thereof is:
4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide (Example 333), or a salt thereof such as a pharmaceutically acceptable salt thereof.
Example 333 is believed to consist essentially of an enantiomer which is believed to have the (R)-stereochemistry at the benzylic carbon atom. See Example 333 below for the believed structure. Example 333 or a salt thereof can for example be for inhaled administration e.g. to a mammal such as human, and/or can be contained in a pharmaceutical composition suitable and/or adapted for inhaled administration, and/or can be in a particle-size-reduced form (e.g. in a size-reduced form obtained or obtainable by micronisation, e.g. see "Particle size reduction" section below).

According to one optional embodiment of the invention, the compound of formula (I) or salt thereof can be a compound of Formula (XXVIII) or a salt thereof:



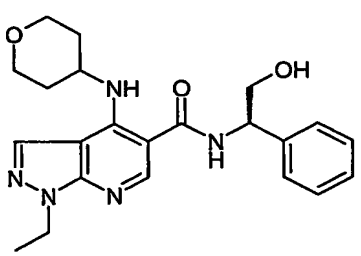
(XXVIII)

wherein:
R^{X1} is a hydrogen atom (H), C_{1-2}alkyl or C_1fluoroalkyl (preferably H);
R^{Y1} is a hydrogen atom (H) or C_{1-2}alkyl;
R^{Y2} is a hydrogen atom (H); C_{1-3}alkyl (e.g. C_{1-2}alkyl or methyl); or $-(CH_2)_n{}^{7aa}$-OH; wherein n^{7aa} is 1, 2 or 3;
and
R^{X2} is Ar^A, wherein:
(i) Ar^A is phenyl optionally substituted by one or two substituents independently being: fluoro, chloro, bromo, C_{1-2}alkyl, C_{1-2}fluoroalkyl, C_{1-2}alkoxy, C_{1-2}fluoroalkoxy; OH; $-NR^{11aa}R^{11bb}$ (wherein R^{11aa} is H or C_{1-2}alkyl and R^{11bb} is H, C_{1-2}alkyl, $-C(O)-C_{1-2}$alkyl or $-S(O)_2-C_{1-2}$alkyl); cyano; $-C(O)-NR^{11cc}R^{11dd}$ (wherein R^{11cc} and R^{11dd} independently are H or C_{1-2}alkyl); $-C(O)-OR^{11ee}$ wherein

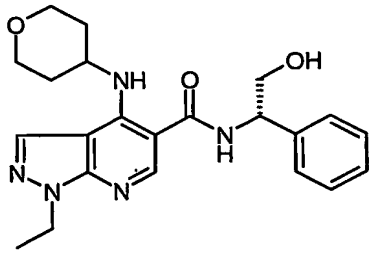
R^{11ee} is H or C_{1-2}alkyl; or $-S(O)_2-R^{11ff}$ (wherein R^{11ff} is C_{1-2}alkyl, NH_2, NHMe or NMe_2); or the phenyl Ar^A is optionally substituted at two adjacent Ar ring atoms by the two ends of a chain which is: $-(CH_2)_4-$, $-(CH_2)_3-$, or -CH=CH-CH=CH-; or

(ii) Ar^A is an optionally substituted 5-membered heterocyclic aromatic ring containing 1, 2, 3 or 4 heteroatoms (e.g. 1, 2 or 3 heteroatoms) selected from O, N or S; and wherein when the heterocyclic aromatic ring Ar^A contains 2, 3 or 4 heteroatoms (e.g. 2 or 3 heteroatoms), one is selected from O, N and S and the remaining heteroatom(s) are N; and wherein the heterocyclic aromatic ring Ar^A is optionally substituted by one or two groups independently being C_{1-4}alkyl (e.g. C_{1-2}alkyl) or OH (including any keto tautomer of an OH-substituted aromatic ring).

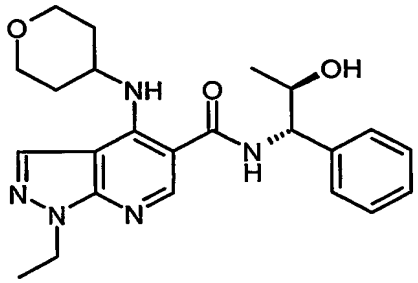
A compound of formula (XXVIII) can suitably be:



,



, or



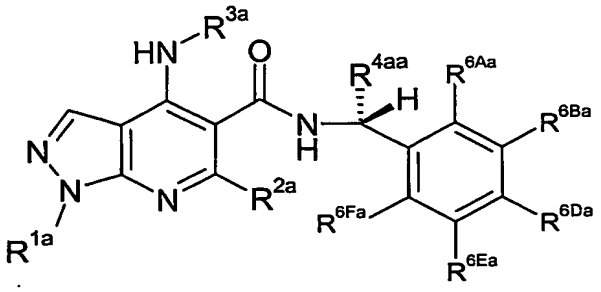
.

These three compounds are:
1-Ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide,
1-Ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide, and
1-Ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide.

These three compounds are disclosed as Intermediates 42, 43 and 46 respectively in copending international patent application PCT/EP2003/014867 (=PCT/EP03/14867), filed on 19 December 2003 in the name of Glaxo Group Limited and published on 8 July 2004 as WO 2004/056823 A1, the content of which is incorporated herein by reference. The compounds of Formula (XXVIII) are also disclosed in PCT/EP2003/014867 (e.g. see page 59 thereof) and are incorporated herein by reference.

According to an alternative optional embodiment of the invention, the compound of formula (I) or salt thereof is not a compound of Formula (XXVIII) or a salt thereof.

A further aspect of the present invention provides a compound of formula (IB) or a salt thereof (in particular, a pharmaceutically acceptable salt thereof):



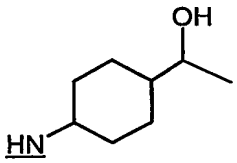
(IB)

wherein:

R^{1a} is C_{2-3}alkyl, C_2fluoroalkyl or $-CH_2CH_2OH$;

R^{2a} is a hydrogen atom (H) or methyl;

NHR^{3a} is of sub-formula (p14), in which the -NH- connection point of the NHR^{3a} group to the 4-position of the pyrazolopyridine of formula (IB) is underlined:



(p14)

R^{4aa} is methyl, ethyl, C_1fluoroalkyl (such as CF_3), $-CH_2OH$, or $-CH_2OMe$;

R^{6Aa}, R^{6Ba}, R^{6Da}, R^{6Ea} and R^{6Fa}, independently of each other, are: a hydrogen atom (H), a fluorine, chlorine, bromine or iodine atom, methyl, ethyl, n-propyl, isopropyl, isobutyl, trifluoromethyl, $-CH_2OH$, methoxy, ethoxy, n-propoxy, isopropoxy, C_1fluoroalkoxy (e.g. trifluoromethoxy or difluoromethoxy), nitro ($-NO_2$), OH, C_{1-3}alkylS(O)$_2$- such as MeS(O)$_2$-, C_{1-2}alkylS(O)$_2$-NH- such as Me-S(O)$_2$-NH-, $-CONH_2$, cyano (-CN), or C_{1-2}alkylS(O)$_2$-CH_2- such as Me-S(O)$_2$-CH_2;

provided that two or more (e.g. three or more) of R^{6Aa}, R^{6Ba}, R^{6Da}, R^{6Ea} and R^{6Fa} are a hydrogen atom (H);

and wherein, in Formula (IB), on a molarity basis, more than 50% of the compound or salt present has the stereochemistry shown at the carbon atom bearing the R^{4aa} group.

In R^{1a}, C_{2-3}alkyl can for example be ethyl or n-propyl. In R^{1a}, C_2fluoroalkyl can for example be C_1fluoroalkyl-CH_2- such as CF_3-CH_2-. Preferably, R^{1a} is ethyl, n-propyl or -CH_2CH_2OH. R^{1a} is most preferably ethyl.

R^{2a} can for example be H.

The NHR^{3a} group of sub-formula (p14) is preferably in the *cis* configuration, i.e. is a [*cis*-4-(1-hydroxyethyl)cyclohexyl]amino group (including mixtures of configurations wherein the *cis* configuration is the major component).

Preferably, R^{4aa} is methyl, ethyl, CF_3 or -CH_2OH; more preferably R^{4aa} is methyl or ethyl; most preferably R^{4aa} is ethyl.

Preferably, R^{6Aa}, R^{6Ba}, R^{6Da}, R^{6Ea} and/or R^{6Fa}, independently of each other, is or are: a hydrogen atom (H), a fluorine, chlorine or bromine atom, methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, -CH_2OH, methoxy, ethoxy, n-propoxy, difluoromethoxy, OH or $MeS(O)_2$-.

Preferably, three or more of R^{6Aa}, R^{6Ba}, R^{6Da}, R^{6Ea} and R^{6Fa} are a hydrogen atom (H).

In formula (IB), the phenyl ring attached to -(CHR^{4aa})- is suitably unsubstituted, monosubstituted, disubstituted or trisubstituted; or preferably the phenyl ring is unsubstituted, monosubstituted or disubstituted; more preferably monosubstituted or disubstituted.

In formula (IB), for monosubstitution of the phenyl ring, then preferably either R^{6Ba} or R^{6Da} is a fluorine, chlorine or bromine atom, methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, -CH_2OH, methoxy, ethoxy, n-propoxy, difluoromethoxy, OH or $MeS(O)_2$- (preferably a fluorine, chlorine or bromine atom, methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, methoxy, ethoxy or difluoromethoxy) and the remainder of R^{6Aa}, R^{6Ba}, R^{6Da}, R^{6Ea} and R^{6Fa} are H. Alternatively, for monosubstitution of the phenyl ring in formula (II), then preferably R^{6Aa} can be a fluorine or chlorine atom, methyl, ethyl, trifluoromethyl, methoxy or difluoromethoxy, and R^{6Ba}, R^{6Da}, R^{6Ea} and R^{6Fa} are H.

In formula (IB), for disubstitution of the phenyl ring, then 3,4-disubstitution, 2,4-disubstitution, 2,3-disubstitution, 2,5-disubstitution or 3,5-disubstitution of the phenyl ring is suitable. For example, in formula (IB), the phenyl ring can be

3,4-dimethylphenyl (R^{6Ba} and R^{6Da} are methyl, and R^{6Aa}, R^{6Ea} and R^{6Fa} are H) or 2,4-dimethylphenyl (R^{6Aa} and R^{6Da} are methyl, and R^{6Ba}, R^{6Ea} and R^{6Fa} are H) or 2,5-dimethylphenyl (R^{6Aa} and R^{6Ea} are methyl, and R^{6Ba}, R^{6Da} and R^{6Fa} are H) or 3,5-dimethylphenyl (R^{6Ba} and R^{6Ea} are methyl, and R^{6Aa}, R^{6Da} and R^{6Fa} are H) or 2-fluoro-4-chlorophenyl (R^{6Aa} is a fluorine atom, R^{6Da} is a chlorine atom, and R^{6Ba}, R^{6Ea} and R^{6Fa} are H) or 3-chloro-4-methylphenyl (R^{6Ba} is a chlorine atom and R^{6Da} is methyl, and R^{6Aa}, R^{6Ea} and R^{6Fa} are H).

In Formula (IB), on a molarity basis, preferably 70% or more, more preferably 75% or more, still more preferably 85% or more, yet more preferably 90% or more, for example 95% or more such as 98% or more, of the compound or salt present has the stereochemistry shown at the carbon atom bearing the R^{4aa} group.

Preferably, in Formula (IB), the stereochemistry at the carbon atom bearing the R^{4aa} group is such that there is an enantiomeric excess (e.e.) of 50% or more at the carbon atom bearing the R^{4aa} group (ignoring the stereochemistry at any other carbon atoms). More preferably, the enantiomeric excess (e.e.) is 70% or more or 80% or more, still more preferably 90% or more, yet more preferably 95% or more, at the carbon atom bearing the R^{4aa} group (ignoring the stereochemistry at any other carbon atoms). As stated before, "enantiomeric excess" (e.e.) is defined as the percentage of the major isomer present minus the percentage of the minor isomer present. For example, if 95% of major isomer is present and 5% of the minor isomer is present, then the e.e. would be 90%.

The compound formula (IB) or the salt thereof is preferably 4-{[*cis*-4-(1-hydroxyethyl)cyclohexyl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide or a salt thereof (e.g. a pharmaceutically acceptable salt thereof), having more than 50% by molarity in the (R)-stereochemistry at the benzylic carbon atom. See for example Example 373 hereinafter.

All references hereinafter to salts, solvates, isomers, tautomeric forms, molecular weights, synthetic process routes, medical uses, pharmaceutical compositions and dosing, and combinations, etc. can also relate to / include the compound formula (IB) or the salt thereof as an alternative to the compound formula (I) or the salt thereof.

Salts, solvates, isomers, tautomeric forms, molecular weights, etc.

Because of their potential use in medicine, the salts of the compounds of formula (I) are preferably pharmaceutically acceptable. Suitable pharmaceutically acceptable salts can include acid or base addition salts.

A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, nitric, phosphoric, succinic, maleic, formic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamaic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, formate, acetate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2- naphthalenesulfonate) or hexanoate salt.

A pharmaceutically acceptable base addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic base (e.g. triethylamine, ethanolamine, triethanolamine, choline, arginine, lysine or histidine), optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration.

Other suitable pharmaceutically acceptable salts include pharmaceutically acceptable metal salts, for example pharmaceutically acceptable alkali-metal or alkaline-earth-metal salts such as sodium, potassium, calcium or magnesium salts; in particular pharmaceutically acceptable metal salts of one or more carboxylic acid moieties that may be present in the the compound of formula (I).

Other non-pharmaceutically acceptable salts, eg. oxalates, may be used, for example in the isolation of compounds of the invention, and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I).

Also included within the scope of the invention are all solvates, hydrates and complexes of compounds and salts of the invention.

Certain groups, substituents, compounds or salts included in the present invention may be present as isomers. The present invention includes within its scope all such isomers, including racemates, enantiomers and mixtures thereof.

In the compounds or salts, pharmaceutical compositions, uses, methods of treatment/prophylaxis, methods of preparing, etc. according to the present invention, where a defined isomeric configuration e.g. stereochemical configuration is described or claimed, the invention includes a mixture comprising (a) a major component of the compound or salt which is in the described or claimed configuration, together with (b) one or more minor components of the compound or salt which is/are not in the described or claimed configuration. Preferably, in such a mixture, the major component of the compound or salt which is in the described or claimed configuration represents 70% or more, or 75% or more, more preferably 85% or more, still more preferably 90% or more,

yet more preferably 95% or more, yet more preferably 98% or more, of the total amount of compound or salt present in the mixture on a molarity basis.

The percentage of one isomeric / stereochemical component in a mixture of different isomeric / stereochemical components, and if appropriate enantiomeric and/or diastereomeric excesses, can be measured using techniques known in the art. Such methods include the following:

(1) Measurement using NMR (e.g. ^{1}H NMR) spectroscopy in the presence of chiral agent. One can measure a nuclear magnetic resonance (NMR) spectrum (preferably a ^{1}H NMR spectrum, and/or a solution-phase NMR spectrum e.g. in $CDCl_3$ or D6-DMSO solvent) of the compound/salt mixture in the presence of a suitable chiral agent which "splits" the NMR peaks of a given atom in different isomers into different peak positions. The chiral agent can be: i) an optically pure reagent which reacts with the compound/salt e.g. to form a mixture of diastereomers, ii) a chiral solvent, iii) a chiral molecule which forms a transient species (e.g. diastereomeric species) with the compound/salt, or iv) a chiral shift reagent. See e.g. J. March, "Advanced Organic Chemistry", 4th edn., 1992, pages 125-126 and refs. 138-146 cited therein. A chiral shift reagent can be a chiral lanthanide shift reagent such as tris[3-trifluoroacetyl-*d*-camphorato]europium-(III) or others as described in Morrill, "Lanthanide Shift Reagents in Stereochemical Analysis", VCH, New York, 1986. Whatever the chiral agent is that is used, usually, the relative integrals (intensities) for the NMR peaks of a given atom or group in different isomers can provide a measurement of the relative amounts of each isomer present.

(2) Measurement using chiral chromatography, especially on an analytical scale. A suitable chiral column which separates the different isomeric components can be used to effect separation, e.g. using gas or liquid chromatography such as HPLC, and/or e.g. on an analytical scale. The peaks for each isomer can be integrated (area under each peak); and a comparison or ratio of the integrals for the different isomers present can give a measurement of the percentage of each isomeric component present. See for example: "Chiral Chromatography", Separation Science Series Author: T.E. Beesley and R.P.W. Scott, John Wiley & Sons, Ltd., Chichester, UK, 1998, electronic Book ISBN: 0585352690, Book ISBN: 0471974277.

(3) Separation of pre-existing diastereomeric mixtures which are compounds/salts of the invention can be achieved (usually directly, without derivatisation) using separation techniques such as gas or liquid chromatography. Diastereomeric ratios and/or excesses can thereby be derived e.g. from the relative peak areas or relative separated masses.

(4) Conversion with a chiral / optically-active agent and subsequent separation of the resulting isomers, e.g. diastereomers. Conversion can be via derivatisation of a derivatisable group (e.g. -OH, -NHR) on the compound/salt with an optically-active derivatising group (e.g. optically active acid chloride or acid anhydride); or can be via formation of an acid or base addition salt of the compound by treatment of the compound with an optically-active acid or base, such as + or – di-para-toluoyl tartaric acid. After derivatisation, separation of the resulting isomers e.g. diastereomers, can be using gas or

liquid chromatography (usually non-chiral); or (especially with isomeric salts) can be by selective crystallisation of a single isomeric e.g. diastereoisomeric salt. Determination of isomeric ratios and/or excesses can be using chromatography peak areas or measurement of mass of each separated isomer.

See e.g. J. March, "Advanced Organic Chemistry", 4th edn., 1992, pages 120-121 and 126, and refs. 105-115 and 147-149 cited therein.

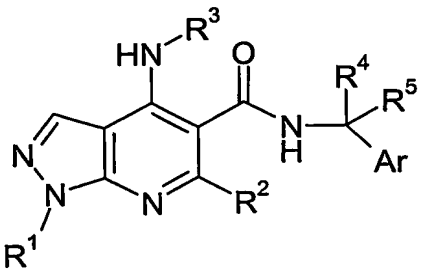
(5) Measurement of optical activity [alpha] of mixture and comparison with optical activity of pure isomer $[alpha]_{max}$ if available (e.g. see J. March, "Advanced Organic Chemistry", 4th edn., 1992, page 125 and refs. 138-139 cited therein). This assumes a substantially linear relationship between [alpha] and concentration.

Certain of the groups, e.g. heteroaromatic ring systems, included in compounds of formula (I) or their salts may exist in one or more tautomeric forms. The present invention includes within its scope all such tautomeric forms, including mixtures.

Especially when intended for oral medicinal use, the compound of formula (I) can optionally have a molecular weight of 1000 or less, for example 800 or less, in particular 650 or less or 600 or less. Molecular weight here refers to that of the unsolvated "free base" compound, that is excluding any molecular weight contributed by any addition salts, solvent (e.g. water) molecules, etc.

Synthetic Process Routes

The following processes can be used to make the compounds of the invention:



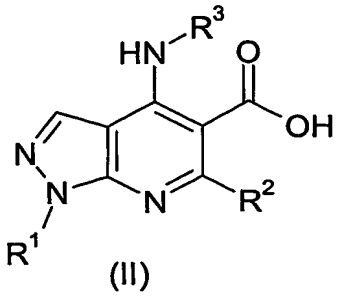
(I)

Some of the following synthetic processes may be exemplified for compounds of Formula (I) wherein R^2 is a hydrogen atom (H). However, some or all of these processes can also be used with appropriate modification, e.g. of starting materials and reagents, for making compounds of Formula (I) wherein R^2 is methyl.

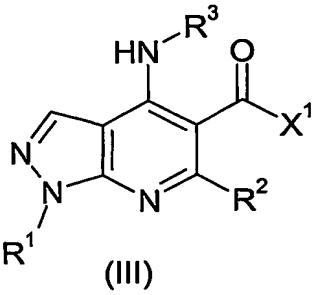
Process A

To form a compound of formula (I), a carboxylic acid of formula (II) can be converted into an activated compound of formula (III) wherein X^1 is a leaving group substitutable

by an amine (as defined below), and subsequently the activated compound can be reacted with an amine of formula $ArCR^4R^5NH_2$:

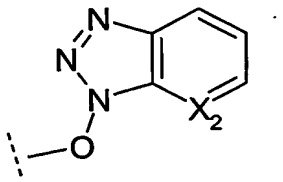


(II)



(III)

For example, the activated compound (the compound of formula (III)) can be the acid chloride (X^1 = Cl). This can be formed from the carboxylic acid of formula (II) e.g. by reaction with thionyl chloride, either in an organic solvent such as chloroform or without solvent. Alternatively, the activated compound (the compound of formula (III)) can be an activated ester wherein the leaving group X^1 is



X_2 = CH or N

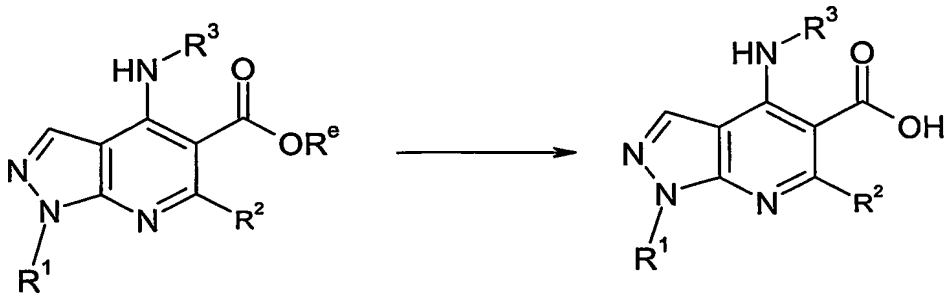
The latter activated compound of formula (III) can be formed from the carboxylic acid of formula (II) either:

(a) by reaction of the carboxylic acid with a carbodiimide such as EDC, which is 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide and is also 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or a salt thereof e.g. hydrochloride salt,
preferably followed by reaction of the resulting product with 1-hydroxybenzotriazole (HOBT); reaction (a) usually being carried out in the presence of a solvent (preferably anhydrous) such as dimethyl formamide (DMF) or acetonitrile and/or preferably under anhydrous conditions and/or usually at room temperature (e.g. about 20 to about 25 °C);

or:

(b) by reaction with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) or O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) ,in the presence of a base such as diisopropylethylamine ($^iPr_2NEt$ = DIPEA), and usually in the presence of a solvent such as dimethyl formamide (DMF) or acetonitrile and/or preferably under anhydrous conditions and/or usually at room temperature (e.g. about 20 to about 25 °C).

Compounds of formula (II) can be prepared by hydrolysis of a compound of formula (IV), an ester:

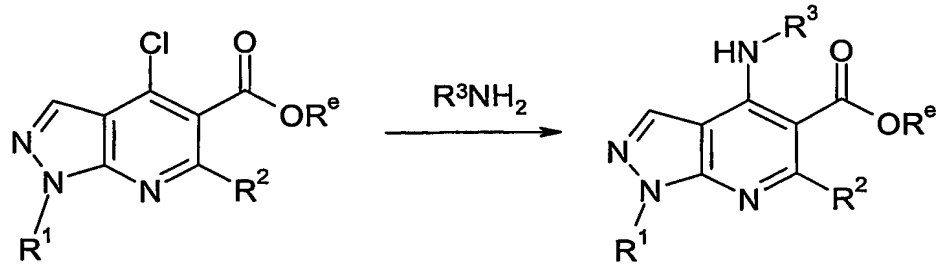


(IV) (II)

This process preferably involves reaction of compound of formula (IV) with either:

(a) a base, such as sodium hydroxide or potassium hydroxide, in a solvent, e.g. an aqueous solvent such as aqueous ethanol or aqueous dioxane or
(b) an acid, such as hydrochloric acid, in a solvent, e.g. an aqueous solvent such as aqueous dioxane.

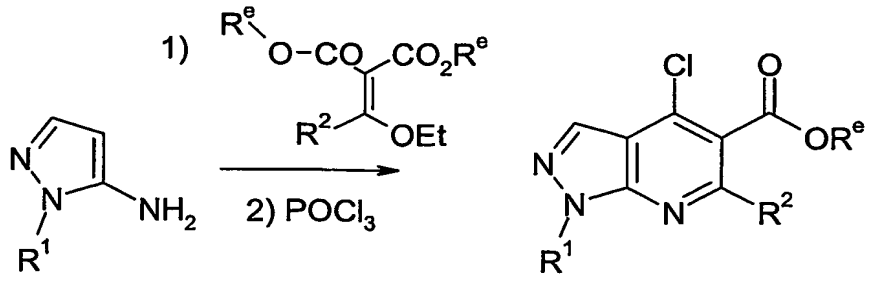
Compounds of formula (IV) can be prepared according to a method, for example as described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027, by reaction of a compound of formula (V) with an amine of formula R^3NH_2. The reaction is preferably carried out in the presence of a base such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, dioxane or acetonitrile. The reaction may require heating e.g. to ca. 60-100°C, for example ca. 80-90°C:



(V) (IV)

Compounds of formula (V) are also described in the above reference. They can be prepared by reaction of a compound of formula (VI) with $(R^2)(OEt)C{=}C(CO_2R^e)_2$, which can for example be diethyl(ethoxymethylene)malonate (wherein R^2 is H and R^e is

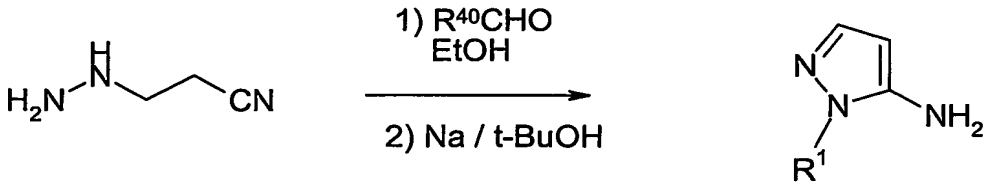
Et) or diethyl 2-(1-ethoxyethylidene)malonate (wherein R^2 is Me and R^e is Et), with heating, followed by reaction with phosphorous oxychloride, again with heating:



(VI) (V)

For examples of the compound (VI) to compound (V) process, see for example: (i) the Intermediate 1 synthesis and G. Yu et. al., *J. Med Chem.*, 2001, 44, 1025-1027 hereinafter, where R^2 = H and R^1 = ethyl; and see (ii) the Intermediate 10 synthesis hereinafter where R^2 = Me and R^1 = ethyl; and see (iii) Intermediate 182 synthesis hereinafter wherein R^2 = H and R^1 = methyl (i.e. reaction of 5-amino-1-methyl pyrazole with diethylethoxymethylene malonate).

Where the desired amino pyrazole of formula (VI) is not commercially available, preparation of the amino pyrazole (VI) can be achieved, for example, using methods described by Dorgan et. al. in *J. Chem. Soc., Perkin Trans. 1*, (4), 938-42; 1980, by reaction of cyanoethyl hydrazine with a suitable aldehyde of formula $R^{40}CHO$ in a solvent such as ethanol, with heating, followed by reduction, for example reduction with sodium in a solvent such as t-butanol. R^{40} should be chosen so as to contain one less carbon atom than R^1, for example R^{40} = methyl will afford R^1 = ethyl.



(VI)

Alternatively, e.g. where the desired amino pyrazole of Formula (VI) is not commercially available, preparation of the 4-amino 5-ester/acid compounds of Formulae (IV) and (II) can be achieved from a (different R^1) 4-chloro 5-ester compound of Formula (V) (e.g. Intermediate 1, wherein R^1 = ethyl), using a generalised version of the reaction scheme shown in Intermediate 170 and shown below. In this method:

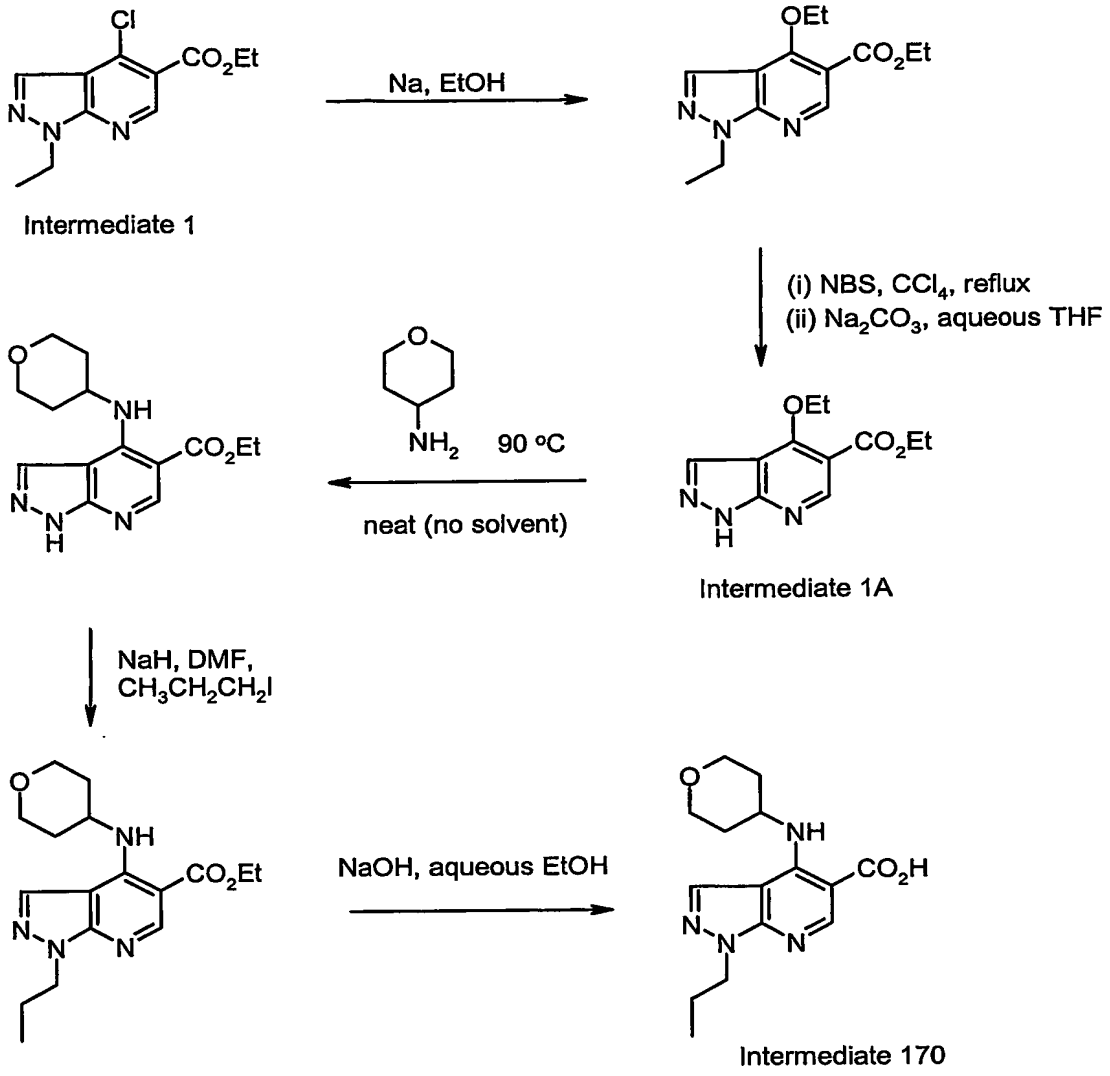
- the 4-chloro 5-ester pyrazolopyridine of Formula (V) (e.g. Intermediate 1) is optionally converted to the 4-alkoxy (e.g. C_{1-4}alkoxy such as ethoxy) pyrazolopyridine;

- the R^1 group is removed (e.g. using N-bromosuccinimide (NBS) and preferably base e.g. Na_2CO_3) (e.g. to give Intermediate 1A – an alternative synthesis for which is given under "Intermediate 1A" hereinafter);

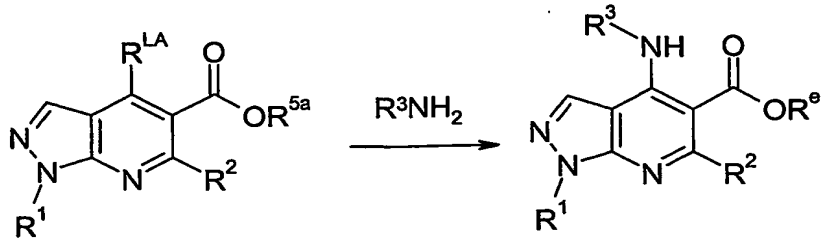
- the 4-amino NHR^3 group is inserted by displacing the 4-chloro or 4-alkoxy group by reaction with R^3NH_2;

- and the resulting pyrazolopyridine is alkylated at N-1 by reacting it with R^1-X^{41}, where X^{41} is a group displaceable by the N-1 nitrogen of the pyrazolopyridine, in order to re-insert the desired R^1 group [i.e. to prepare the 4-amino 5-ester compound of Formula (IV)]. X^{41} can for example be a halogen, e.g. Cl, Br or I; or X^{41} can be -O-S(O)$_2$-R^{41} where R^{41} is C_{1-4}alkyl, C_{1-2}fluoroalkyl, or phenyl optionally substituted by C_{1-2}alkyl. The N-1 alkylation reation with R^1-X^{41} is preferably carried out in the presence of base – see the (IX) to (IV) reaction hereinafter for examples of suitable bases.

The scheme below (Intermediate 170 scheme) shows a suitable exemplary route and conditions for this R^1 removal and re-insertion route, for insertion of R^1 = n-propyl and R^3 = tetrahydro-2H-pyran-4-yl:

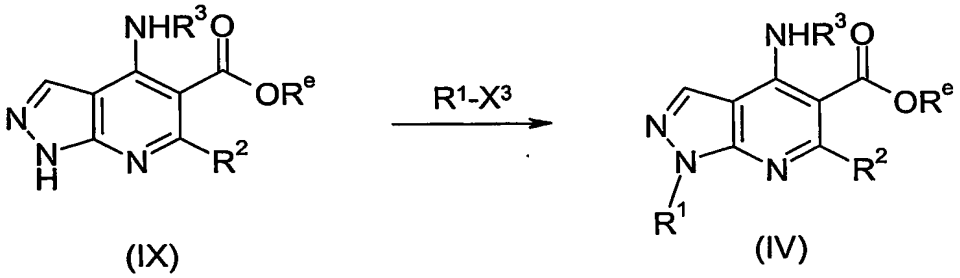


In an alternative embodiment of Process A, the 4-chloro substituent in the compound of formula (V) can be replaced by another halogen atom, such as a bromine atom, or by another suitable leaving group which is displaceable by an amine of formula R^3NH_2. The leaving group displaceable by the amine can for example be R^{LA}, in a compound of formula (Va), wherein R^{LA} is an alkoxy group OR^{35} such as OC_{1-4}alkyl (in particular OEt) or a group $-O-S(O)_2-R^{37}$. Here, R^{37} is C_{1-8}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl such as methyl), C_{1-6}fluoroalkyl (e.g. C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as CF_3 or C_4F_9), or phenyl wherein the phenyl is optionally substituted by one or two of independently C_{1-2}alkyl, halogen or C_{1-2}alkoxy (such as phenyl or 4-methyl-phenyl). The reaction of the compound of formula (Va) with the amine of formula R^3NH_2 may be carried out with or without solvent and may require heating:



(Va) (IV)

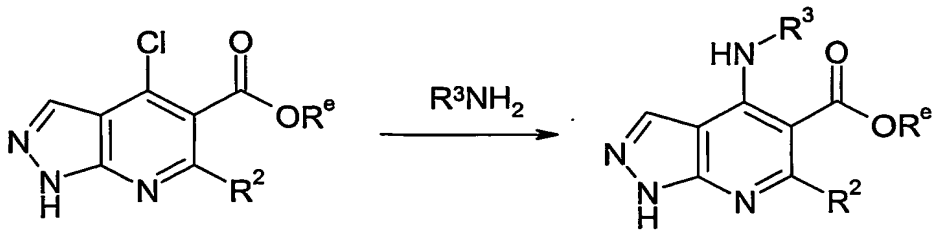
In another alternative embodiment of Process A, the compound of formula (IV), described herein, can be prepared by reaction of a compound of formula (IX) with an alkylating agent of formula R^1-X^3, where X^3 is a leaving group displaceable by the 1-position pyrazolopyridine nitrogen atom of the compound of formula (IX):



(IX) (IV)

A suitable alkylating agent of formula R^1-X^3 can be used. For example, X^3 can be a halogen atom such as a chlorine atom or more preferably a bromine or iodine atom, or X^3 can be –O-S(O)$_2$-R^{36} wherein R^{36} is C_{1-8}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl such as methyl), C_{1-6}fluoroalkyl (e.g. C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as CF_3 or C_4F_9), or phenyl wherein the phenyl is optionally substituted by one or two of independently C_{1-2}alkyl, halogen or C_{1-2}alkoxy (such as phenyl or 4-methyl-phenyl). The reaction is preferably carried out in the presence of a base; the base can for example comprise or be potassium carbonate, sodium carbonate, sodium hydride, potassium hydride, or a basic resin or polymer such as polymer-bound 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine. The reaction is preferably carried out in the presence of a solvent, e.g. an organic solvent such as DMF; the solvent is preferably anhydrous.

Compounds of formula (IX) can be prepared, using a method analogous to that used for the preparation of compounds of formula (IV) from compounds of formula (V), by reaction of a compound of formula (X) (which is the same as compound of formula (V) but wherein R^1 = H) with an amine of formula R^3NH_2. The reaction is suitably carried out in the presence of a base such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, dioxane or acetonitrile. The reaction may require heating e.g. to ca. 60-100°C, for example ca. 80-90°C:

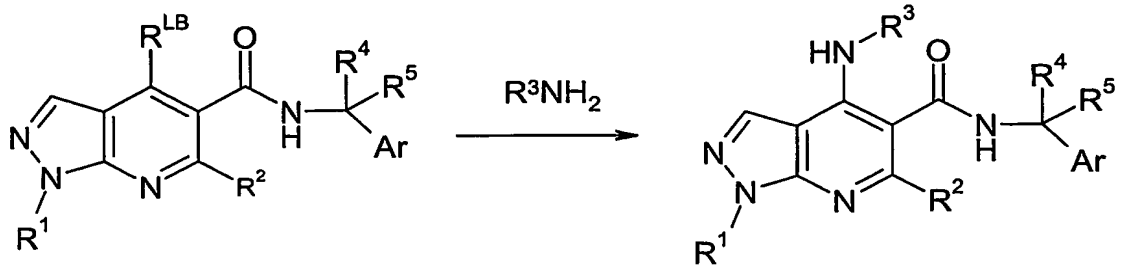


(X) (IX)

Alternatively, in formula (X), the 4-chloro can be replaced by 4-C_{1-4}alkoxy such as 4-ethoxy; these modified compounds, of formula (Xa), can optionally be made as described above, e.g. see the Intermediate 170 scheme shown and described above or Intermediate 1A below.

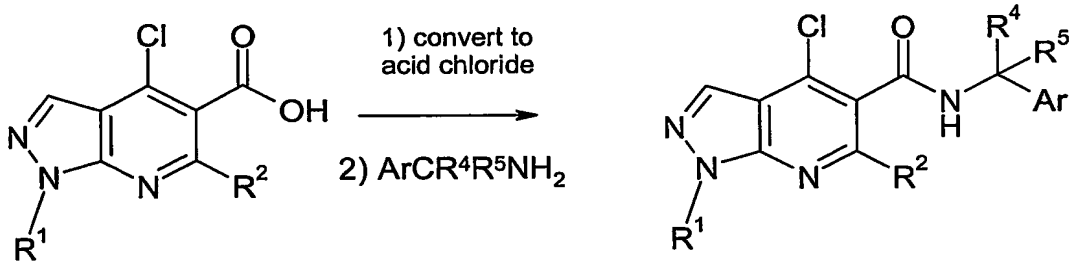
Process B

Compounds of formula (I) can be prepared by reaction of a compound of formula (VII) with an amine of formula R^3NH_2. In the compound of formula (VII), R^{LB} is a leaving group which is displaceable by the amine of formula R^3NH_2. R^{LB} can be a bromine atom (Br) or more particularly a chlorine atom (Cl), or alternatively R^{LB} can be an alkoxy group OR^{35} such as OC_{1-4}alkyl (in particular OEt) or a group -O-S(O)$_2$-R^{37}. Here, R^{37} is C_{1-8}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl such as methyl), C_{1-6}fluoroalkyl (e.g. C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as CF_3 or C_4F_9), or phenyl wherein the phenyl is optionally substituted by one or two of independently C_{1-2}alkyl, halogen or C_{1-2}alkoxy (such as phenyl or 4-methyl-phenyl). The reaction of (VII) to (I) is preferably carried out in the presence of a base, such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, THF, dioxane or acetonitrile. The reaction may require heating, e.g. to ca. 60-100 °C or ca. 80-90 °C, for example for 8-48 or 12-24 hours:



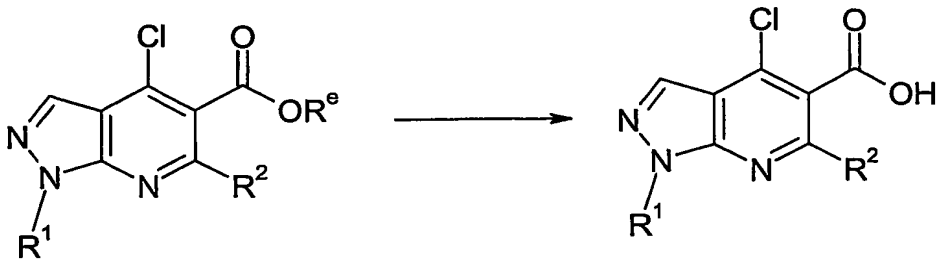
(VII) (I)

Compounds of formula (VII), wherein R^{LB} is a chlorine atom (compound of formula (VIIa), can be prepared in a two step procedure as described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573. This process involves 2 steps. In the first step, a compound of formula (VIII) is reacted with thionyl chloride (or another agent suitable for forming an acid chloride from a carboxylic acid), either in an organic solvent such as chloroform or THF, or as a neat solution. This reaction may require heating and the thus-formed intermediate may or may not be isolated. Step two involves reaction with an amine of formula $ArCR^4R^5NH_2$, in an organic solvent such as THF or chloroform and may also involve the use of a base such as triethylamine or diisopropylethylamine:



(VIII) (VIIa)

Compounds of formula (VIII) can be prepared by hydrolysis of an ester of formula (V) according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027. This procedure preferably involves reaction with a base, such as sodium hydroxide or potassium hydroxide, in a solvent e.g. an aqueous solvent such as aqueous ethanol or aqueous dioxane:

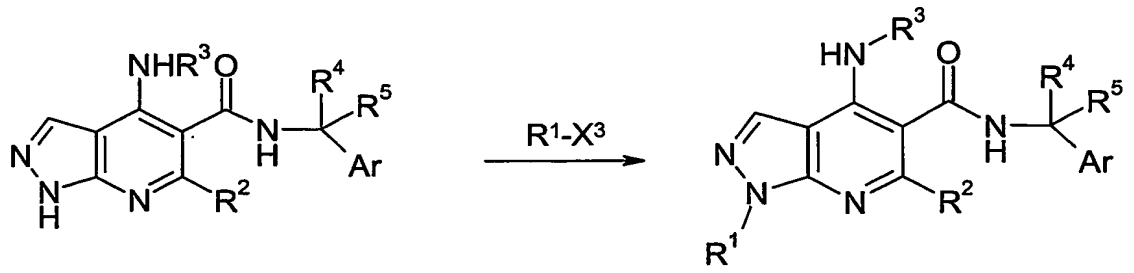


(V) (VIII)

Compounds of formula (V) can be prepared as described in Process A above.

Process C

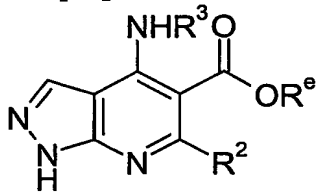
A compounds of formula (I) can be prepared by reaction of a compound of formula (IXa) with an alkylating agent of formula R^1-X^3, where X^3 is a leaving group displaceable by the 1-position pyrazolopyridine nitrogen atom of the compound of formula (IXa):



(IXa) (I)

A suitable alkylating agent of formula R^1-X^3 can be used. For example, X^3 can be a halogen atom such as a chlorine atom or more preferably a bromine or iodine atom, or X^3 can be –O-S(O)$_2$-R^{36} wherein R^{36} is C_{1-8}alkyl (e.g. C_{1-4}alkyl or C_{1-2}alkyl such as methyl), C_{1-6}fluoroalkyl (e.g. C_{1-4}fluoroalkyl or C_{1-2}fluoroalkyl such as CF_3 or C_4F_9), or phenyl wherein the phenyl is optionally substituted by one or two of independently C_{1-2}alkyl, halogen or C_{1-2}alkoxy (such as phenyl or 4-methyl-phenyl). The reaction is preferably carried out in the presence of a base; the base can for example comprise or be potassium carbonate, sodium carbonate, sodium hydride, potassium hydride, or a basic resin or polymer such as polymer-bound 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine. The reaction is preferably carried out in the presence of a solvent, e.g. an organic solvent such as DMF; the solvent is preferably anhydrous.

Compounds of formula (IXa) can be prepared from a compound of formula (IX):



(IX)

by hydrolysis of the ester and conversion of the resulting carboxylic acid to the amide of formula (IXa) by activation of the acid and reaction with an amine of formula $ArCR^4R^5NH_2$. The ester (IX) to acid to amide (IXa) conversion can suitably use the reagents and reaction conditions mentioned in Process A above for conversion of (IV) to (II) to (III) to (I).

The ester compound of formula (IX) can be prepared using the method described in the alternative embodiment of Process A, above.

Process D: *Conversion of one compound of formula (I), (II) or (IV) or salt thereof into another compound of formula (I), (II) or (IV) or salt thereof*

One compound of formula (I), (II) or (IV) or salt thereof (or a protected version thereof, such as an N-protected version e.g. BOC-N-protected) can be converted into a or another compound of formula (I), (II) or (IV) or salt thereof. This conversion preferably comprises or is one or more of the following processes D1 to D7:

D1. Conversion of a ketone into the corresponding oxime (e.g. Examples 231-281).

D2. An oxidation process. For example, the oxidation process can comprise or be oxidation of an alcohol to a ketone (e.g. using Jones reagent) or oxidation of an alcohol or a ketone to a carboxylic acid. The oxidation process can e.g. comprise or be conversion of a nitrogen-containing compound of formula (I) or salt thereof to the corresponding N-oxide (e.g. using *meta*-chloroperoxybenzoic acid), for example conversion of a pyridine-containing compound to the corresponding pyridine N-oxide (e.g. see Examples 210-212 of PCT/EP03/11814 (WO 2004/024728 A2), filed on 12 September 2003 and incorporated herein by reference, for suitable process details).

D3. A reduction process, for example reduction of a ketone or a carboxylic acid to an alcohol.

D4. Acylation, for example acylation of an amine (e.g. see Examples 329-349 and Example 353 of PCT/EP03/11814 (WO 2004/024728 A2), filed on 12 September 2003 and incorporated herein by reference, for suitable process details), or acylation of a hydroxy group.

D5. Alkylation, for example alkylation of an amine or of a hydroxy group.

D6. Hydrolysis, e.g. hydrolysis of an ester to the corresponding carboxylic acid or salt thereof (e.g. see Examples 351, 488, 489, 650, 651 of PCT/EP03/11814 (WO 2004/024728 A2), filed on 12 September 2003 and incorporated herein by reference, for suitable process details).

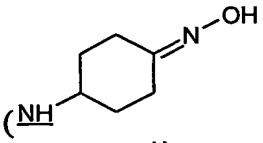
D7. Deprotection, e.g. deprotection of (e.g. deacylation of or t-butyloxycarbonyl (BOC) removal from) an amine group. BOC deprotection can be carried out under acidic conditions e.g. using hydrogen chloride in an organic solvent such as dioxan – Examples 381 and 382 herein are examples of such a BOC deprotection process.

D8. Formation of an ester or amide, for example from the corresponding carboxylic acid.

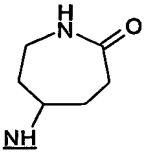
D9. Sulfonylation, e.g. sulfonamide formation by reaction of an amine with a sulfonyl halide e.g. a sulfonyl chloride (e.g. see Examples 322-328 of PCT/EP03/11814 (WO 2004/024728 A2), filed on 12 September 2003 and incorporated herein by reference, for suitable process details).

and/or

D10. Beckmann rearrangement of one compound of formula (I) into another compound of formula (I), for example using cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) together with a formamide such as DMF, e.g. at room temperature (see L.D. Luca, *J. Org. Chem.*, 2002, 67, 6272-6274). The Beckmann rearrangement can for example comprise conversion of a compound of formula (I) wherein NHR^3 is of sub-formula (o2)

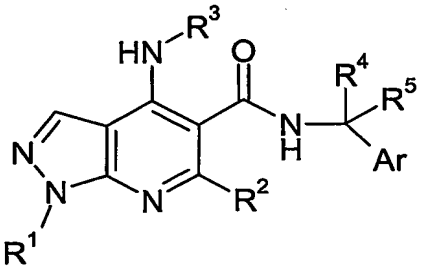


( ) into a compound of formula (I) wherein NHR^3 is of sub-formula



(m3) ( ), and suitable process details can be as illustrated in Examples 658 and 659 of PCT/EP03/11814 (WO 2004/024728 A2), filed on 12 September 2003 and incorporated herein by reference.

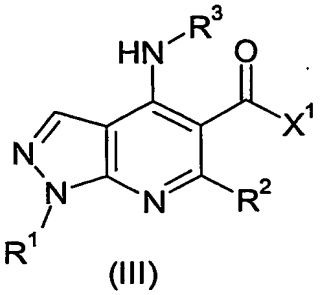
The present invention therefore also provides a method of preparing a compound of formula (I) or a salt thereof:



(I)

wherein R^1, R^2, R^3, R^4, R^5 and Ar are as defined herein, the method comprising :

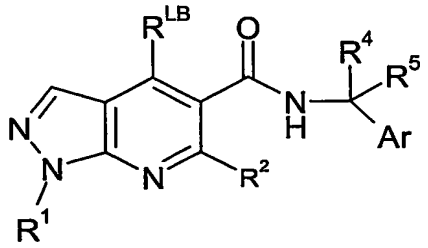
(a) reaction of an activated compound of formula (III),



(III)

wherein X^1 is a leaving group substitutable by an amine, with an amine of formula $ArCR^4R^5NH_2$;

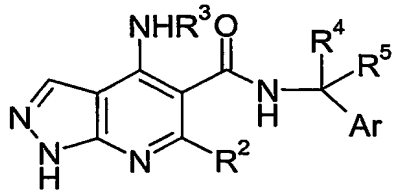
(b) reaction of a compound of formula (VII):



(VII)

, wherein R^{LB} is a leaving group which is displaceable by an amine of formula R^3NH_2, with an amine of formula R^3NH_2;

(c) reaction of a compound of formula (IXa) with an alkylating agent of formula R^1-X^3, where X^3 is a leaving group displaceable by the 1-position pyrazolopyridine nitrogen atom of the compound of formula (IXa):



(IXa) ;

or

(d) conversion of one compound of formula (I) or salt thereof (or a protected version thereof, such as an N-protected version e.g. BOC-N-protected) into a or another compound of formula (I) or salt thereof;

and optionally converting the compound of formula (I) into a salt thereof e.g. a pharmaceutically acceptable salt thereof.

Preferred, suitable or optional features of methods (a), (b), (c) and (d), independently of each other, are as described above for Processes A, B, C, and D, with all necessary changes being made.

The present invention also provides: (e) a method of preparing a pharmaceutically acceptable salt of a compound of formula (I) comprising conversion of the compound of formula (I) or a salt thereof into the desired pharmaceutically acceptable salt thereof. (See for example Example 307 herein).

The present invention also provides a compound of formula (I) or a salt thereof, prepared by a method as defined herein.

Medical uses

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal such as a human. The compound or salt can be for use in the treatment and/or prophylaxis of any of the diseases / conditions described herein (e.g. for use in the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human; or e.g. for use in the treatment and/or prophylaxis of cognitive impairment or depression in a mammal such as a human) and/or for use as a phosphodiesterase inhibitor e.g. for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (e.g. pharmaceutical composition) for the treatment and/or prophylaxis of any of the diseases / conditions described herein in a mammal such as a human, e.g. for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human, or e.g. for the treatment and/or prophylaxis of cognitive impairment or depression in a mammal.

Also provided is a method of treatment and/or prophylaxis of any of the diseases / conditions described herein in a mammal (e.g. human) in need thereof, e.g. a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease, cognitive impairment or depression in a mammal (e.g. human) in need thereof, which method comprises administering to the mammal (e.g. human) a therapeutically effective amount

of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

Phosphodiesterase 4 inhibitors are thought to be useful in the treatment and/or prophylaxis of a variety of diseases / conditions, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic obstructive pulmonary disease (COPD) (e.g. chronic bronchitis and/or emphysema), atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, multiple sclerosis, cognitive impairment (e.g. in a neurological disorder such as Alzheimer's disease), depression, or pain (e.g. inflammatory pain). Ulcerative colitis and/or Crohn's disease are collectively often referred to as inflammatory bowel disease.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease can suitably be chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis, allergic rhinitis or atopic dermatitis in a mammal (e.g. human). In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is suitably chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis in a mammal (e.g. human). More preferably, the treatment and/or prophylaxis is of COPD or asthma in a mammal (e.g. human).

PDE4 inhibitors are thought to be effective in the treatment of asthma (e.g. see M.A.Giembycz, *Drugs*, Feb. 2000, 59(2), 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; P.J. Barnes, *Naure Reviews - Drug Discovery*, October 2004, 831-844; and references cited in the aforementioned publications).

PDE4 inhibitors, for example cilomilast and roflumilast, are thought to be effective in the treatment of COPD. For example, see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; A.M. Vignola, *Respiratory Medicine*, 2004, 98, 495-503; D. Spina, *Drugs*, 2003, 63(23), 2575-2594; and references cited in the aforementioned publications; and G. Krishna et al., *Expert Opinion on Investigational Drugs*, 2004, 13(3), 255-267 (see especially pp. 259-261 and refs. 102-111 and 201 therein). COPD is often characterised by the presence of airflow obstruction due to

chronic bronchitis and/or emphysema (e.g., see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319).

PDE4 inhibitors are thought to be effective in the treatment of allergic rhinitis (e.g. see B.M. Schmidt et al., *J. Allergy & Clinical Immunology*, 108(4), 2001, 530-536).

PDE4 inhibitors are thought to be effective in the treatment of rheumatoid arthritis and multiple sclerosis (e.g. see H.J.Dyke et al., *Expert Opinion on Investigational Drugs*, January 2002, 11(1), 1-13; C.Burnouf et al., *Current Pharmaceutical Design*, 2002, 8(14), 1255-1296; and A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473; and references cited in these publications).

See e.g. A.M.Doherty, *Current Opinion Chem. Biol.*, 1999, 3(4), 466-473 and references cited therein for atopic dermatitis use.

For treatment and/or prophylaxis of atopic dermatitis, topical administration (e.g. topical administration to the skin e,g. to affected skin) can be used.

PDE4 inhibitors have been suggested as having analgesic properties and thus being effective in the treatment of pain (A.Kumar et al., *Indian J. Exp. Biol.*, 2000, 38(1), 26-30).

In the invention, the treatment and/or prophylaxis can be of cognitive impairment e.g. cognitive impairment in a neurological disorder such as Alzheimer's disease. For example, the treatment and/or prophylaxis can comprise cognitive enhancement e.g. in a neurological disorder. See for example: H.T.Zhang et al. in: *Psychopharmacology*, June 2000, 150(3), 311-316 and *Neuropsychopharmacology*, 2000, 23(2), 198-204; and T. Egawa et al., *Japanese J. Pharmacol.*, 1997, 75(3), 275-81.

PDE4 inhibitors such as rolipram have been suggested as having antidepressant properties (e.g. J. Zhu et al., *CNS Drug Reviews*, 2001, 7(4), 387-398; O'Donnell, *Expert Opinion on Investigational Drugs*, 2000, 9(3), 621-625; H.T. Zhang et al., *Neuropsychopharmacology*, October 2002, 27(4), 587-595; J. M. O'Donnell and H.-T. Zhang, *Trends Pharmacol. Sci.*, March 2004, 25(3), 158-163; and T.E.Renau, *Curr. Opinion Invest. Drugs*, 2004, 5(1), 34-39).

PDE4 inhibition has been suggested for the treatment of inflammatory bowel disease (e.g. ulcerative colitis and/or Crohn's disease), see K.H.Banner and M.A.Trevethick, *Trends Pharmacol. Sci.*, August 2004, 25(8), 430-436.

Pharmaceutical compositions and dosing

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

The invention also provides a method of preparing a pharmaceutical composition comprising a compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers and/or excipients,

the method comprising mixing the compound or salt with the one or more pharmaceutically acceptable carriers and/or excipients.

The invention also provides a pharmaceutical composition prepared by said method.

The compounds of formula (I) and/or the pharmaceutical composition may be administered, for example, by oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled, topical (e.g. skin topical), or nasal administration. Accordingly, the pharmaceutical composition is preferably suitable for oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled, topical (e.g. skin topical), or nasal administration.

More preferably, the pharmaceutical composition is suitable for inhaled or oral administration, e.g. to a mammal such as a human. Inhaled administration involves topical administration to the lung e.g. by aerosol or dry powder composition.

A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a syrup, suspension or emulsion, a tablet, a capsule or a lozenge.

A liquid formulation (e.g. oral) will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

In one embodiment, the pharmaceutical composition is in unit dose form, such as a tablet or capsule for oral administration, e.g. for oral administration to a human.

A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. The carrier can for example be or include lactose, cellulose (for example microcrystalline cellulose), or mannitol. The tablet can also or instead contain one or more pharmaceutically acceptable excipients, for example a binding agent such as hydroxypropylmethylcellulose or povidone (polyvinylpyrrolidone), a lubricant

e.g. an alkaline earth metal stearate such as magnesium stearate, and/or a tablet disintegrant such as sodium starch glycollate, croscarmellose sodium, or crospovidone (cross-linked polyvinylpyrrolidone). The pharmaceutical composition being a tablet can be prepared by a method comprising the steps of: (i) mixing the compound of formula (I), as herein defined, or a pharmaceutically acceptable salt thereof, with the one or more pharmaceutically acceptable carriers and/or excipients, (ii) compressing the resulting mixture (which is usually in powder form) into tablets, and (iii) optionally coating the tablet with a tablet film-coating material.

A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets or powder containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous gum or an oil and the dispersion or suspension then filled into a soft gelatin capsule.

A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution can be lyophilised; the lyophilised parenteral pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

A topical pharmaceutical composition, e.g. skin topical pharmaceutical composition, can for example be an ointment, a cream (i.e. an oil-in-water pharmaceutical composition), an aqueous gel, or a DMSO-containing solution such as a DMSO/acetone solution (DMSO = dimethyl sulphoxide). A topical pharmaceutical composition, e.g. an oil-in-water composition, can optionally include a skin-penetration enhancer such as propylene glycol, and/or (e.g. for an oil-in-water composition) an emulsifier (e.g. surfactant) such as sodium dodecyl sulphate (SDS). A topical ointment can for example comprise polyethylene glycol and/or propylene glycol. In a topical pharmaceutical composition, such as an ointment or an oil-in-water composition, the compound of formula (I) or the salt thereof can optionally be present at 0.25 to 5%, for example 0.5 to 2.5%, by weight of the total composition. In a topical pharmaceutical composition, the compound of formula (I) or the salt thereof can optionally be Example 73, 75, 98, 283, 304, 306, 307, 310, 311, 316, 321, 324, 326, 327, 328, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 343, 344 or 345, as the compound or a pharmaceutically acceptable salt thereof. A topical pharmaceutical composition, e.g. skin topical pharmaceutical composition, can for example be for treatment and/or prophylaxis of atopic dermatitis e.g. in a mammal such as a human.

Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, drops, gels or dry powders.

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for

use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide, or an organic propellant such as a chlorofluorocarbon (CFC) or hydrofluorocarbon (HFC). Suitable CFC propellants include dichlorodifluoromethane, trichlorofluoromethane and dichlorotetrafluoroethane. Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser.

Particle size reduction of compound of formula (I) or salt thereof

For use in, for example, pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or salt of formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. Micronisation usually involves subjecting the compound/salt to collisional and/or abrasional forces in a fast-flowing circular or spiral/vortex-shaped airstream often including a cyclone component. The preferable particle size of the size-reduced (e.g. micronised) compound or salt is defined by a D50 value of about 0.5 to about 10 microns, e.g. about 1 to about 7 microns or about 1 to about 5 microns (e.g. as measured using laser diffraction). For example, it is preferable for the compound or salt of formula (I) to have a particle size defined by: a D10 of about 0.3 to about 3 microns (e.g. about 0.5 to about 2 microns, or about 1 micron), and/or a D50 of about 0.5 to about 10 microns or about 1 to about 7 microns or (e.g. about 1 to about 5 microns or about 2 to about 5 microns or about 2 to about 4 microns), and/or a D90 of about 1 to about 30 microns or about 2 to about 20 microns or about 2 to about 15 microns or about 3 to about 15 microns (e.g. about 5 to about 15 microns or about 5 to about 10 microns or about 2 to about 10 microns); for example as measured using laser diffraction.

In particle size measurements, D90, D50 and D10 respectively mean that 90%, 50% and 10% of the material is less than the micron size specified. D50 is the median particle size. DV90, DV50 and DV10 respectively mean that 90%, 50% and 10% by volume of the material is less than the micron size specified. DM90, DM50 and DM10 respectively mean that 90%, 50% and 10% by weight of the material is less than the micron size specified.

Laser diffraction measurement of particle size can use a dry method (wherein a suspension of the compound/salt in an airflow crosses the laser beam) or a wet method [wherein a suspension of the compound/salt in a liquid dispersing medium, such as isooctane or (e.g. if compound is soluble in isooctane) 0.1% Tween 80 in water, crosses

the laser beam]. With laser diffraction, particle size is preferably calculated using the Fraunhofer calculation; and/or preferably a Malvern Mastersizer or Sympatec apparatus is used for measurement. For example, particle size measurement and/or analysis by laser diffraction can use any or all of (preferably all of) the following: a Malvern Mastersizer longbed version, a dispersing medium of 0.1% Tween 80 in water, a stir rate of ca. 1500 rpm, ca. 3 mins sonification prior to final dispersion and analysis, a 300 RF (Reverse Fourier) lens, and/or the Fraunhofer calculation with Malvern software.

An illustrative non-limiting example of a small-scale micronisation process is now given:

Micronisation Examples: Micronisation of Example 73, 75, 98, 283, 304, 306, 307, 308, 309, 310, 311, 312, 313, 314, 314A or 333

- Purpose: To micronise Example 73, 75, 98, 283, 304, 306, 307, 308, 309, 310, 311, 312, 313, 314 or 314A or 333 (described hereinafter), usually in an amount of approximately 600-1000 mg thereof, using a Jetpharma MC1 micronizer.
- The parent (unmicronised) and micronised materials are analyzed for particle size by laser diffraction and crystallinity by PXRD.

Equipment and material

Equipment/material	Description and specification
Jetpharma MC1 Micronizer	Nitrogen supply: Air tank with 275psi rate tubing
Analytical balance	Sartorius Analytical
Top loader balance	Mettler PM400
Digital Caliper	VWR Electronic caliper
Materials to be micronised (Procedure 1 - carried out)	Example 307
Materials to be micronised (alternative embodiments of Procedure 1 - carried out)	Example 73, Example 75, Example 283 or Example 333
Materials to be micronised (Procedure 2 – not carried out)	Example 73, 98, 283, 304, 306, 307, 308, 309, 310, 311, 312, 313, 314 or 314A

The Jetpharma MC1 Micronizer comprises a horizontal disc-shaped milling housing having: a tubular compound inlet (e.g. angled at ca. 30 degrees to the horizontal) for entry of a suspension of unmicronised compound of formula (I) or salt in a gasflow, a separate gas inlet for entry of gases, a gas outlet for exit of gases, and a collection vessel (micronizer container) for collecting micronised material. The milling housing has two chambers: (a) an outer annular chamber in gaseous connection with the gas inlet, the chamber being for receiving pressurised gas (e.g. air or nitrogen), and (b) a disc-shaped inner milling chamber within and coaxial with the outer chamber for micronising the

input compound / salt, the two chambers being separated by an annular wall. The annular wall (ring R) has a plurality of narrow-bored holes connecting the inner and outer chambers and circumferentially-spaced-apart around the annular wall. The holes opening into the inner chamber are directed at an angle (directed part-way between radially and tangentially), and in use act as nozzles directing pressurised gas at high velocity from the outer chamber into the inner chamber and in an inwardly-spiral path (vortex) around the inner chamber (cyclone). The compound inlet is in gaseous communication with the inner chamber via a nozzle directed tangentially to the inner chamber, within and near to the annular wall / ring R. Upper and lower broad-diameter exit vents in the central axis of the inner milling chamber connect to (a) (lower exit) the collection vessel which has no air outlet, and (b) (upper exit) the gas outlet. Inside and coaxial with the tubular compound inlet and longitudinally-movable within it is positioned a venturi inlet (V) for entry of gases. The compound inlet also has a bifurcation connecting to an upwardly-directed material inlet port for inputting material.

In use, the narrow head of the venturi inlet (V) is preferably positioned below and slightly forward of the material inlet port, so that when the venturi delivers pressurised gas (e.g. air or nitrogen) the feed material is sucked from the material inlet port into the gas stream through the compound inlet and is accelerated into the inner milling chamber tangentially at a subsonic speed. Inside the milling chamber the material is further accelerated to a supersonic speed by the hole/nozzle system around the ring (R) (annular wall) of the milling chamber. The nozzles are slightly angled so that the acceleration pattern of the material is in the form of an inwardly-directed vortex or cyclone. The material inside the milling chamber circulates rapidly and particle collisions occur during the process, causing larger particles to fracture into smaller ones. "Centrifugal" acceleration in the vortex causes the larger particles to remain at the periphery of the inner chamber while progressively smaller particles move closer to the centre until they exit the milling chamber, generally through the lower exit, at low pressure and low velocity. The particles that exit the milling chamber are heavier than air and settle downward thorugh the lower exit into the collection vessel (micronizer container), while the exhaust gas rises (together with a minority of small particles of micronised material) and escapes into the atmosphere at low pressure and low velocity.

Procedure:

The micronizer is assembled. The narrow head of the venturi inlet is positioned below and slightly forward of the material inlet port and is measured with a micro-caliper to make sure that it is inserted correctly. The ring (R) and venturi (V) pressures are adjusted according to the values specified in the experimental design (refer to experimental section below) by adjusting the valves on the pressure gauges on the micronizer. The setup is checked for leakage by observing if there is any fluctuation in the reading of the pressure gauges.

Note that the venturi (V) pressure is kept at least 2 bars greater than the ring (R) pressure to prevent regurgitation of material, e.g. outwardly from the material inlet port.

Balance performance is checked with calibration weights. Specified amount of the parent material (see e.g. section on experimental run Procedure 1 for Example 307) is fed into the input container of the micronizer using a spatula. The input container plus material is weighed. The equipment pressure is monitored during the micronization process.

Upon completion of the micronising run, the nitrogen supply is shut off and the micronised material is allowed to settle into the micronizer container. The micronised powder in the micronizer container (collection vessel) and the cyclone (above the recovery vessel) are collected together into a pre-weighed and labelled collection vial. The weight of the micronised material is recorded. The input container is re-weighed in order to calculate the amount of input material by difference. The micronizer is disassembled and residual PDE4 compound on the micronizer inner surface is rinsed with 70/30 isopropyl alcohol / water and collected into a flask. The micronizer is then thoroughly cleaned in a Lancer washing machine and dried before subsequent runs are performed.

Optional Experimental Parameters

Procedure 1: *Experimental Parameters and Results for* ***Example 307***

This experiment, Procedure 1, using Example 307 as the compound to be micronised, has been carried out generally using a procedure and an apparatus generally as described above or similar to those described, using generally the following experimental parameters and giving the following results:

Procedure no.	Material input amount (g)	Venturi Pressure (V) / ring (R) Pressure (bar)	Particle Size Data (microns) (unmicronised material)	Particle Size Data (microns) (micronised material)	Recovery yield of micronised material*
1	ca. 0.9 g	V = 5 to 7 bar R = 3 to 4 bar	D10 = 2.48 D50 = 8.98 D90 = 24.14	D10 = 0.84 D50 = 1.56 D90 = 2.74	58%

*% yield = [(Material from collection vessel + Material from cyclone) / Material input amount] x100.

In general, very approximately 50-75% yields are achievable using this method, including material from collection vessel and material from inside walls of cyclone.

The above optional parameters can be varied using the skilled person's knowledge.

In alternative embodiments of Procedure 1, Procedure 1 or variations thereof generally using generally similar conditions, have also been carried out for the following Examples:
Example 73

Example 75
Example 283
Example 333.

Procedure 2: *Optional Experimental Parameters*
Parent (unmicronised) material (Procedure 2): Example 73, 98, 283, 304, 306, 307, 308, 309, 310, 311, 312, 313, 314 or 314A (note – not carried out)
Balance(s): Sartorius analytical

Procedure no.	Material input amount (g)	Venturi Pressure (V) / ring (R) Pressure (bar)	Intended feed-rate	Notes
2	ca. 0.9 g	V = 8 to 10 bar R = 5.5 to 6 bar	180 to 200 mg/min	Note that this Procedure 2 was not carried out

The above optional parameters can be varied using the skilled person's knowledge.

Procedure 2 includes possible parameters and conditions, and micronisation of possible Examples, and has not been carried out.

Alternative embodiment: Any of the Examples of the compounds or salts of the invention disclosed herein are optionally micronised as described above.

Dry powder inhalable compositions

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose or starch, the compound of formula (I) or salt thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine, mannitol, trehalose and/or magnesium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of formula (I) or salt thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less

than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. Most importantly, it is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanzeplein 25, 8017 JD Zwolle, Netherlands).

In the dry powder inhalable composition, preferably, the compound of formula (I) or salt thereof is present in about 0.1% to about 70% (e.g. about 1% to about 50%, e.g. about 5% to about 40%, e.g. about 20 to about 30%) by weight of the composition.

An illustrative non-limiting example of a dry powder inhalable composition follows:

Dry Powder Formulation Example - Dry powder Lactose Blend Preparation

Using a size-reduced e.g. micronised form of the compound of formula (I) or salt thereof (e.g. as prepared in the Micronisation Example above), the dry powder blend is prepared by mixing the required amount of the compound/salt (e.g. 10 mg, 1% w/w) with inhalation-grade lactose containing 10% fines (e.g. 990 mg, 99% w/w) in a Teflon™ (polytetrafluoroethene) pot in a Mikro-dismembrator ball-mill (but without a ball bearing) at ¾ speed (ca. 2000-2500 rpm) for about 4 hours at each blend concentration. The Mikro-dismembrator (available from B. Braun Biotech International, Schwarzenberger Weg 73-79, D-34212 Melsungen, Germany; www.bbraunbiotech.com) comprises a base with an upwardly-projecting and sidewardly-vibratable arm to which is attached the Teflon ™ pot. The vibration of the arm achieves blending.

Other blends can include: 10% w/w compound/salt (50 mg) + 90% w/w lactose (450 mg, inhalation-grade lactose containing 10% fines).

Serial dilution of the 1% w/w blend can achieve e.g. 0.1% and 0.3% w/w blends.

Dry powder inhalation devices

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (e.g. containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose, e.g. of the dry powder composition, can be administered by inhalation via a device such as the DISKUS ™ device, marketed by GlaxoSmithKline. The DISKUS ™ inhalation device is usually substantially as described in GB 2,242,134 A. In such device at least one container for the pharmaceutical composition in powder form (the at least one container preferably being a plurality of sealed dose containers mounted longitudinally in a strip or ribbon) is defined between two members peelably secured to one another; the device comprises: means defining an opening station for the said at least one container; means for peeling the members apart at the opening station to open the container; and an outlet, communicating with the opened container, through

which a user can inhale the pharmaceutical composition in powder form from the opened container.

Unit dose form and dosing regimens

Preferably the composition is in unit dose form such as a tablet or capsule for oral administration, e.g. for oral administration to a human.

In the pharmaceutical composition, a or each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. A or each dosage unit for nasal or inhaled administration preferably contains from 0.001 to 50 mg, more preferably 0.01 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

A pharmaceutically acceptable compound or salt of the invention is preferably administered to a mammal (e.g. human) in a daily oral or parenteral dose of 0.001 mg to 50 mg per kg body weight per day (mg/kg/day), for example 0.01 to 20 mg/kg/day or 0.03 to 10 mg/kg/day or 0.1 to 2 mg/kg/day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

A pharmaceutically acceptable compound or salt of the invention is preferably administered to a mammal (e.g. human) in a daily nasal or inhaled dose of: 0.0001 to 5 mg/kg/day or 0.0001 to 1 mg/kg/day, e.g. 0.001 to 1 mg/kg/day or 0.001 to 0.3 mg/kg/day or 0.001 to 0.1 mg/kg/day or 0.005 to 0.3 mg/kg/day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds or salts of the invention is preferably administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day e.g. 2 to 500 mg per day, or a nasal or inhaled dose of 0.001 to 300 mg per day or 0.001 to 50 mg per day or 0.01 to 30 mg per day or 0.01 to 5 mg per day or 0.02 to 2 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

Combinations

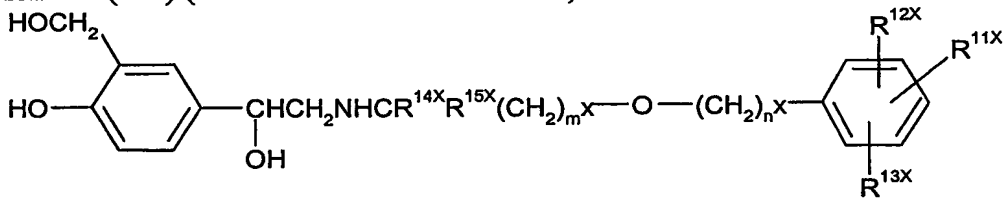
The compounds, salts and/or pharmaceutical compositions according to the invention may also be used in combination with another therapeutically active agent, for example, a β_2 adrenoreceptor agonist, an anti-histamine, an anti-allergic or an anti-inflammatory agent.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another therapeutically active agent, for example, a β_2-adrenoreceptor agonist, an anti-histamine, an anti-allergic, an anti-inflammatory agent or an antiinfective agent.

Preferably, the β_2-adrenoreceptor agonist is salmeterol (e.g. as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline, or a salt thereof (e.g. pharmaceutically acceptable salt thereof), for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. Long-acting β_2-adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 12-24 hour period such as salmeterol or formoterol. Preferably, the β_2-adrenoreceptor agonist is for inhaled administration, e.g. once per day and/or for simultaneous inhaled administration; and more preferably the β_2-adrenoreceptor agonist is in particle-size-reduced form e.g. as defined herein. Preferably, the β_2-adrenoreceptor agonist combination is for treatment and/or prophylaxis of COPD or asthma. Salmeterol or a pharmaceutically acceptable salt thereof, e.g. salmeterol xinofoate, is preferably administered to humans at an inhaled dose of 25 to 50 micrograms twice per day (measured as the free base). The combination with a β_2-adrenoreceptor agonist can be as described in WO 00/12078.

Preferred long acting β_2-adrenoreceptor agonists include those described in WO 02/066422A, WO 03/024439, WO 02/070490 and WO 02/076933.

Especially preferred long-acting β_2-adrenoreceptor agonists include compounds of formula(XX) (described in WO 02/066422):



(XX)

or a salt or solvate thereof, wherein in formula (XX):
m^X is an integer of from 2 to 8;
n^X is an integer of from 3 to 11,
with the proviso that $m^X + n^X$ is 5 to 19,
R^{11X} is $-XSO_2NR^{16X}R^{17X}$ wherein X is $-(CH_2)_{p^x}-$ or C_{2-6} alkenylene;
R^{16X} and R^{17X} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $C(O)NR^{18X}R^{19X}$, phenyl, and phenyl (C_{1-4}alkyl)-,
or R^{16X} and R^{17X}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7-membered nitrogen containing ring, and R^{16X} and R^{17X} are each optionally substituted by one or two groups selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, hydroxy-substituted C_{1-6}alkoxy, $-CO_2R^{18X}$, $-SO_2NR^{18X}R^{19X}$, $-CONR^{18X}R^{19X}$, $-NR^{18X}C(O)R^{19X}$, or a 5-, 6- or 7-membered heterocylic ring;
R^{18X} and R^{19X} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, and phenyl (C_{1-4}alkyl)-; and
p^X is an integer of from 0 to 6, preferably from 0 to 4;

R^{12X} and R^{13X} are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and
R^{14X} and R^{15X} are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^{14X} and R^{15X} is not more than 4.

Preferred β_2-adrenoreceptor agonists disclosed in WO 02/066422 include:
3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl}amino)hexyl]oxy}butyl)benzenesulfonamide and
3-(3-{[7-({(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)benzenesulfonamide.

A preferred β_2-adrenoreceptor agonist disclosed in WO 03/024439 is:
4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol.

A combination of a compound of formula (I) or salt together with an anti-histamine is preferably for oral administration (e.g. as a combined composition such as a combined tablet), and can be for treatment and/or prophylaxis of allergic rhinitis. Examples of anti-histamines include methapyrilene, or H1 antagonists such as cetirizine, loratadine (e.g. Clarityn ^{TM}), desloratadine (e.g. Clarinex ^{TM}) or fexofenadine (e.g. Allegra ^{TM}).

The invention also provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anticholinergic compound, e.g. a muscarinic (M) receptor antagonist in particular an M_1, M_2, M_1/M_2, or M_3 receptor antagonist, more preferably a M_3 receptor antagonist, still more preferably a M_3 receptor antagonist which selectively antagonises (e.g. antagonises 10 times or more strongly) the M_3 receptor over the M_1 and/or M_2 receptor. For combinations of anticholinergic compounds / muscarinic (M) receptor antagonist with PDE4 inhibitors, see for example WO 03/011274 A2 and WO 02/069945 A2 / US 2002/0193393 A1 and US 2002/052312 A1, and some or all of these publications give examples of anticholinergic compounds / muscarinic (M) receptor antagonists which may be used with the compounds of formula (I) or salts, and/or suitable pharmaceutical compositions. For example, the muscarinic receptor antagonist can comprise or be an ipratropium salt (e.g. ipratropium bromide), an oxitropium salt (e.g. oxitropium bromide), or more preferably a tiotropium salt (e.g. tiotropium bromide); see e.g. EP 418 716 A1 for tiotropium.

The anticholinergic compound or muscarinic (M) receptor antagonist, e.g. M_3 receptor antagonist, is preferably for inhaled administration, more preferably in particle-size-reduced form e.g. as defined herein. More preferably, both the muscarinic (M) receptor antagonist and the compound of formula (I) or the pharmaceutically acceptable salt

thereof are for inhaled administration. Preferably, the anticholinergic compound or muscarinic receptor antagonist and the compound of formula (I) or salt are for simultaneous administration. The muscarinic receptor antagonist combination is preferably for treatment and/or prophylaxis of COPD.

Other suitable combinations include, for example, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with another anti-inflammatory agent such as an anti-inflammatory corticosteroid; or a non-steroidal anti-inflammatory drug (NSAID) such as a leukotriene antagonist (e.g. montelukast), an iNOS inhibitor, a tryptase inhibitor, a elastase inhibitor, a beta-2 integrin antagonist, a adenosine 2a agonist, a CCR3 antagonist, or a 5-lipoxogenase inhibitor; or an antiinfective agent (e.g. an antibiotic or an antiviral). An iNOS inhibitor is preferably for oral administration. Suitable iNOS inhibitors (inducible nitric oxide synthase inhibitors) include those disclosed in WO 93/13055, WO 98/30537, WO 02/50021, WO 95/34534 and WO 99/62875. Suitable CCR3 inhibitors include those disclosed in WO 02/26722.

In a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with an anti-inflammatory corticosteroid (which is preferably for treatment and/or prophylaxis of asthma, COPD or allergic rhinitis), then preferably the anti-inflammatory corticosteroid is fluticasone, fluticasone propionate (e.g. see US patent 4,335,121), beclomethasone, beclomethasone 17-propionate ester, beclomethasone 17,21-dipropionate ester, dexamethasone or an ester thereof, mometasone or an ester thereof, ciclesonide, budesonide, flunisolide, or a compound as described in WO 02/12266 A1 (e.g. as claimed in any of claims 1 to 22 therein), or a pharmaceutically acceptable salt of any of the above. If the anti-inflammatory corticosteroid is a compound as described in WO 02/12266 A1, then preferably it is Example 1 therein {which is 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester} or Example 41 therein {which is 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester}, or a pharmaceutically acceptable salt thereof. The anti-inflammatory corticosteroid is preferably for intranasal or inhaled administration. Fluticasone propionate is preferred and is preferably for inhaled administration to a human either (a) at a dose of 250 micrograms once per day or (b) at a dose of 50 to 250 micrograms twice per day.

Also provided is a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with β_2-adrenoreceptor agonist and an anti-inflammatory corticosteroid, for example as described in WO 03/030939 A1. Preferably this combination is for treatment and/or prophylaxis of asthma, COPD or allergic rhinitis. The β_2-adrenoreceptor agonist and/or the anti-inflammatory corticosteroid can be as described above and/or as described in WO 03/030939 A1. Most preferably, in this "triple" combination, the β_2-adrenoreceptor agonist is salmeterol or a

pharmaceutically acceptable salt thereof (e.g. salmeterol xinafoate) and the anti-inflammatory corticosteroid is fluticasone propionate.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus a pharmaceutical composition comprising a combination as defined above together with one or more pharmaceutically acceptable carriers and/or excipients represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical composition.

In one embodiment, the combination as defined herein can be for simultaneous inhaled administration and is disposed in a combination inhalation device. Such a combination inhalation device is another aspect of the invention. Such a combination inhalation device can comprise a combined pharmaceutical composition for simultaneous inhaled administration (e.g. dry powder composition), the composition comprising all the individual compounds of the combination, and the composition being incorporated into a plurality of sealed dose containers mounted longitudinally in a strip or ribbon inside the inhalation device, the containers being rupturable or peel-openable on demand; for example such inhalation device can be substantially as described in GB 2,242,134 A (DISKUS ^{TM}) and/or as described above. Alternatively, the combination inhalation device can be such that the individual compounds of the combination are administrable simultaneously but are stored separately (or wholly or partly stored separately for triple combinations), e.g. in separate pharmaceutical compositions, for example as described in PCT/EP03/00598 filed on 22 January 2003, published as WO 03/061743 (e.g. as described in the claims thereof e.g. claim 1).

The invention also provides a method of preparing a combination as defined herein,

the method comprising either

(a) preparing a separate pharmaceutical composition for administration of the individual compounds of the combination either sequentially or simultaneously, or

(b) preparing a combined pharmaceutical composition for administration of the individual compounds of the combination simultaneously,

wherein the pharmaceutical composition comprises the combination together with one or more pharmaceutically acceptable carriers and/or excipients.

The invention also provides a combination as defined herein, prepared by a method as defined herein.

BIOLOGICAL TEST METHODS

PDE 3, PDE 4B, PDE 4D, PDE 5, PDE 6 Primary assay methods

The activity of the compounds can be measured in the assay methods shown below. Preferred compounds of the invention are selective PDE4 inhibitors, i.e. they inhibit PDE4 (e.g. PDE4B and/or PDE4D, preferably PDE4B) more strongly than they inhibit PDE3 and/or more strongly than they inhibit PDE5 and/or more strongly than they inhibit PDE6.

Possible PDE enzyme sources and literature references

Human recombinant PDE4B, in particular the 2B splice variant thereof (HSPDE4B2B), is disclosed in WO 94/20079 and also M.M. McLaughlin et al., "A low *K*m, rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA", *J. Biol. Chem.*, 1993, **268**, 6470-6476. For example, in Example 1 of WO 94/20079, human recombinant PDE4B is described as being expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62, e.g. after induction by addition of 150 uM $CuSO_4$, and 100,000 x *g* supernatant fractions of yeast cell lysates are described for use in the harvesting of PDE4B enzyme.

Human recombinant PDE4D (HSPDE4D3A) is disclosed in P. A. Baecker et al., "Isolation of a cDNA encoding a human rolipram-sensitive cyclic AMP phoshodiesterase (PDE IV_D)", *Gene*, 1994, **138**, 253-256.

Human recombinant PDE5 is disclosed in K. Loughney et al., "Isolation and characterisation of cDNAs encoding PDE5A, a human cGMP-binding, cGMP-specific 3',5'-cyclic nucleotide phosphodiesterase", *Gene*, 1998, **216**, 139-147.

PDE3 can be purified from bovine aorta as described by H. Coste and P. Grondin, "Characterisation of a novel potent and specific inhibitor of type V phosphodiesterase", *Biochem. Pharmacol.*, 1995, **50**, 1577-1585.

PDE6 can be purified from bovine retina as described by: P. Catty and P. Deterre, "Activation and solubilization of the retinal cGMP-specific phosphodiesterase by limited proteolysis", *Eur. J. Biochem.*, 1991, **199**, 263-269; A. Tar et al. "Purification of bovine retinal cGMP phosphodiesterase", *Methods in Enzymology*, 1994, **238**, 3-12; and/or D. Srivastava et al. "Effects of magnesium on cyclic GMP hydrolysis by the bovine retinal rod cyclic GMP phosphodiesterase", *Biochem. J.*, 1995, **308**, 653-658.

Inhibition of PDE 3, PDE 4B, PDE 4D, PDE 5 or PDE 6 activity: radioactive Scintillation Proximity Assay (SPA)

The ability of compounds to inhibit catalytic activity at PDE4B or 4D (human recombinant), PDE3 (from bovine aorta), PDE5 (human recombinant) or PDE6 (from bovine retina) can optionally be determined by Scintillation Proximity Assay (SPA) in 96-well format.

Test compounds (as a solution in DMSO, preferably about 2 microlitre (ul) volume of DMSO solution) are preincubated at ambient temperature (room temperature, e.g. 19-23°C) in Wallac Isoplates (code 1450-514) with PDE enzyme in 50mM Tris-HCl buffer pH 7.5 , 8.3mM $MgCl_2$, 1.7mM EGTA, 0.05% (w/v) bovine serum albumin for 10-30 minutes (usually 30 minutes). The enzyme concentration is adjusted so that no more than 20% hydrolysis of the substrate defined below occurs in control wells without compound, during the incubation. For the PDE3, PDE4B and PDE4D assays, [5',8-^{3}H]Adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech, code TRK.559; or Amersham Biosciences UK Ltd, Pollards Wood, Chalfont St Giles, Buckinghamshire HP8 4SP, UK) is added to give 0.05uCi per well and about 10nM final concentration. For the PDE5 and PDE6 assays, [8-^{3}H]Guanosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech, code TRK.392) is added to give 0.05uCi per well and about 36nM final concentration. Plates containing assay mixture, preferably approx. 100 ul volume of assay mixture, are mixed on an orbital shaker for 5 minutes and incubated at ambient temperature for 1 hour. Phosphodiesterase SPA beads (Amersham Pharmacia Biotech, code RPNQ 0150) are added (about 1mg per well) to terminate the assay. Plates are sealed and shaken and allowed to stand at ambient temperature for 35 minutes to 1 hour (preferably 35 minutes) to allow the beads to settle. Bound radioactive product is measured using a WALLAC TRILUX 1450 Microbeta scintillation counter. For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound are assayed. Curves are analysed using ActivityBase and XLfit (ID Business Solutions Limited, 2 Ocean Court, Surrey Research Park, Guildford, Surrey GU2 7QB, United Kingdom) Results are expressed as pIC_{50} values.

In an alternative to the above radioactive SPA assay, PDE4B or PDE4D inhibition can be measured in the following Fluorescence Polarisation (FP) assay:

Inhibition of PDE4B or PDE4D activity: Fluorescence Polarisation (FP) assay

The ability of compounds to inhibit catalytic activity at PDE4B (human recombinant) or PDE4D (human recombinant) can optionally be determined by IMAP Fluorescence Polarisation (FP) assay (IMAP Explorer kit, available from Molecular Devices Corporation, Sunnydale, CA, USA; Molecular Devices code: R8062) in 384-well format.

The IMAP FP assay is able to measure PDE activity in an homogenous, non-radioactive assay format. The FP assay uses the ability of immobilised trivalent metal cations, coated onto nanoparticles (tiny beads), to bind the phosphate group of Fl-AMP that is produced on the hydrolysis of fluorescein-labelled (Fl) cyclic adenosine mono-

phosphate (Fl-cAMP) to the non-cyclic Fl-AMP form. Fl-cAMP does not bind. Binding of Fl-AMP product to the beads (coated with the immobilised trivalent cations) slows the rotation of the bound Fl-AMP and leads to an increase in the fluorescence polarisation ratio of parallel to perpendicular light. Inhibition of the PDE reduces/inhibits this signal increase.

Test compounds (small volume, e.g. ca. 0.5 to 1 ul, preferably ca. 0.5 ul, of solution in DMSO) are preincubated at ambient temperature (room temperature, e.g. 19-23°C) in black 384-well microtitre plates (supplier: NUNC, code 262260) with PDE enzyme in 10mM Tris-HCl buffer pH 7.2, 10mM $MgCl_2$, 0.1% (w/v) bovine serum albumin, and 0.05% NaN_3 for 10-30 minutes. The enzyme level is set by experimentation so that reaction is linear throughout the incubation. Fluorescein adenosine 3',5'-cyclic phosphate (from Molecular Devices Corporation, Molecular Devices code: R7091) is added to give about 40nM final concentration (final assay volume usually ca. 20-40 ul, preferably ca. 20 ul). Plates are mixed on an orbital shaker for 10 seconds and incubated at ambient temperature for 40 minutes. IMAP binding reagent (as described above, from Molecular Devices Corporation, Molecular Devices code: R7207) is added (60ul of a 1 in 400 dilution in binding buffer of the kit stock solution) to terminate the assay. Plates are allowed to stand at ambient temperature for 1 hour. The Fluorescence Polarisation (FP) ratio of parallel to perpendicular light is measured using an Analyst^{TM} plate reader (from Molecular Devices Corporation). For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound are assayed. Curves are analysed using ActivityBase and XLfit (ID Business Solutions Limited, 2 Ocean Court, Surrey Research Park, Guildford, Surrey GU2 7QB, United Kingdom). Results are expressed as pIC_{50} values.

In the FP assay, reagents are usually dispensed using Multidrop^{TM} (available from Thermo Labsystems Oy, Ratastie 2, PO Box 100, Vantaa 01620, Finland).

For a given PDE4 inhibitor, the PDE4B (or PDE4D) inhibition values measured using the SPA and FP assays can differ slightly. However, in a regression analysis of 100 test compounds (not necessarily compounds of the invention), the pIC_{50} inhibition values measured using SPA and FP assays have been found generally to agree within about 0.5 log units, for each of PDE4B and PDE4D (linear regression coefficient 0.966 for PDE4B and 0.971 for PDE4D; David R.Mobbs et al., "Comparison of the IMAP Fluorescence Polarisation Assay with the Scintillation Proximity Assay for Phosphodiesterase Activity", poster presented at 2003 Molecular Devices UK & Europe User Meeting, 2nd October 2003, Down Hall, Harlow, Essex, United Kingdom).

Biological Data obtained for some of the Examples (PDE4B inhibitory activity, either as one reading or as an average of several (e.g. ca. 2-6) readings) are generally as follows, based on measurements only, generally using SPA and/or FP assays generally as described above or generally similar to those described above. In each of the SPA and FP assays, absolute accuracy of measurement is not possible, and the readings given are thought to be accurate only up to about ± 0.5 of a log unit, depending on the number of readings made and averaged:

Example number	PDE4B pIC_{50} (± about 0.5)
1, 8, 24, 28, 63, 75	8.3 to 9.1
6, 7, 26, 29, 64, 25	7.15 to 7.5
13, 50	8.3 to 9.1
2, 37, 38	7.6 to 7.9
48, 73, 98, 139, 191, 210, 218, 221, 252, 261, 282, 283, 304, 306	8.7 to 10.0
Examples 308 to 314, and Examples 368, 369, 379, 380, 382	8.0 to 9.45
Examples 316 to 345	9.0 to 10.1
Examples 346 to 355	8.5 to 9.3
Examples 356 to 359	6.8 to 7.4
Examples 360 to 367	7.2 to 9.0
Examples 370 to 373	6.9 to 7.9
Examples 375 to 378	7.0 to 8.3

A large majority or substantially all of the Examples have been tested for PDE4B inhibition, normally using the radioactive SPA assay and/or the FP assay generally as described above or generally similar to those described above. A large majority or substantially all of the Examples tested have PDE4B inhibitory activities in the range of pIC_{50} = about 6 (± about 0.5) to about 10.1 (± about 0.5). Where an Example is described in the Examples section below as capable of being made using a possible reagent source which is an Intermediate (e.g. which might have a defined or enriched or no benzylic carbon atom (CR4R5) stereochemistry), then, without any guarantee, the PDE4B inhibition pIC50 values mentioned above are thought to be, in general, those obtained for the Example when made using that Intermediate specified in the Examples section.

Only selected ones of the PDE4B-tested Examples have also been tested, on an optional basis, for one or more of: PDE3, PDE5 or PDE6 inhibition using the above-described or other assays.

Of the Examples tested for PDE4B and PDE5 inhibition, those selected Examples wherein R^3 = cyclohexyl (NHR^3 = sub-formula (c)), tetrahydro-2H-pyran-4-yl (NHR^3 = group (h)), 4-oxocyclohexyl (NHR^3 = sub-formula (o)), *cis*-3-hydroxy-cyclohexyl (NHR^3 = sub-formula (n) in *cis* configuration), 4-(hydroxyimino)cyclohexyl (NHR^3 = sub-formula (o2), 4-(aminocarbonyl)cyclohexyl (NHR^3 = sub-formula (p9), especially with majority of *cis* isomer or *cis/trans* mixtures), or 1-(aminocarbonyl)-4-piperidinyl (NHR^3 is of sub-formula (k2)), and wherein R^1 is ethyl, R^2 is H and having preferred

-NH-C(R^4)(R^5)-Ar groups, sometimes or often exhibit selectivity for PDE4B over PDE5, as measured in the above enzyme inhibition assays and/or in generally-similar assays or other assays.

Emesis: Some known PDE4 inhibitors can cause emesis and/or nausea to greater or lesser extents, especially after systemic exposure e.g. after oral administration (e.g. see Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438, see especially pages 433-434 and refs cited therein). Therefore, it would be preferable, but not essential, if a PDE4 inhibitory compound or salt of the invention were to cause only limited or manageable emetic side-effects, e.g. after oral or parenteral administration. Emetic side-effects can for example be measured by the emetogenic potential of the compound or salt when administered to ferrets; for example one can measure the time to onset, extent, frequency and/or duration of vomiting, retching and/or writhing in ferrets after oral or parenteral administration of the compound or salt. See for example In vivo Assay 4 hereinafter for one optional measurement method for anti-inflammatory effect, emetic side-effects and therapeutic index (TI) in the ferret. See also for example A. Robichaud et al., "Emesis induced by inhibitors of [PDE IV] in the ferret", *Neuropharmacology*, 1999, 38, 289-297, erratum *Neuropharmacology*, 2001, 40, 465-465. However, optionally, emetic side-effects and therapeutic index (TI) in rats can be conveniently measured by monitoring the pica feeding behaviour of rats after administration of the compound or salt of the invention (see In Vivo Assay 2 below).

Other side effects: Some known PDE4 inhibitors can cause other side effects such as headache and other central nervous sytem (CNS-) mediated side effects; and/or gastrointestinal (GI) tract disturbances. Therefore, it would be preferable but not essential if a particular PDE4 inhibitory compound or salt of the invention were to cause only limited or manageable side-effects in one or more of these side-effect categories.

Other optional *in vitro* assays:

Inhibition of TNFα (TNF-alpha) Production in Human Whole Blood

This is a useful optional supplementary test, e.g. for potentially orally-administrable PDE4 inhibitors.

Test compounds are prepared as a ca. 10mM stock solution in DMSO and a dilution series prepared in DMSO with 8 successive 3-fold dilutions, either directly from the 10mM stock solution or from a more dilute solution in DMSO. The compound is added to assay plates using a Biomek Fx liquid handling robot.

Heparinised blood drawn from normal volunteers is dispensed (ca. 100µl = ca. 100ul) into microtitre plate wells containing ca. 0.5 or ca. 1.0µl (ul) of an appropriately diluted test compound solution. After ca. 1 hr incubation at ca. 37 °C, 5% CO_2, ca. 25µl (ca.

25ul) of LPS (lipopolysaccharide) solution (S. typhosa) in RPMI 1640 (containing 1% L-glutamine and 1% Penicillin/ streptomycin) is added (ca. 50ng/ml final). The samples are incubated at ca. 37°C, 5% CO_2, for ca. 20 hours, and ca. 100µl (ca. 100ul) physiological saline (0.138% NaCl) is added, and diluted plasma is collected using a Platemate or Biomek FX liquid handling robot after centrifugation at ca. 1300 g for ca. 10 min. Plasma TNFα content is determined by electrochemiluminescence assay using the IGEN technology (see below) or by enzyme linked immunosorbant assay (ELISA) (see below).

Inhibition of TNFα (TNF-alpha) Production in Human PBMC assay

This is a useful optional supplementary test, e.g. for potentially inhalably-administrable PDE4 inhibitors.

Test compounds are prepared as a ca. 10mM stock solution in DMSO and a dilution series prepared in DMSO with 8 successive 3-fold dilutions, either directly from the 10mM stock solution or from a more dilute solution in DMSO. The compound is added to assay plates using a Biomek Fx liquid handling robot.

PBMC cells (monocytes) are prepared from heparinised human blood from normal volunteers by centrifugation on histopaque at ca. 1000g for ca. 30 minutes. The cells are collected from the interface, washed by centrifugation (ca. 1300g, ca. 10 minutes) and resuspended in assay buffer (RPMI1640 containing 10% foetal calf serum, 1% L-glutamine and 1% penicillin/streptomycin) at $1x10^6$ cells/ml. Ca. 50µl (ca. 50ul) cells are added to microtitre wells containing ca. 0.5 or ca/ 1.0µl (ul) of an appropriately diluted compound solution. Ca. 75µl (ul) LPS (ca. 1 ng/ml final) is added and the samples are incubated at 37 °C, 5% CO_2, for 20 hours. The supernatant is removed and the concentrations of TNF are determined by electrochemiluminescence assay using the IGEN technology or by ELISA (see below).

TNFα IGEN Assay

Ca. 50µl supernatant from either whole blood or PBMC assay plates is transferred to a 96 well polypropylene plate. Each plate also contains a TNFα standard curve (ca. 0 to 30000 pg/ml: R+D Systems, 210-TA). Ca. 50µl (ul) of streptavidin/biotinylated anti-TNFα antibody mix, ca. 25µl ruthenium tagged anti-TNFα monoclonal and ca. 100µl PBS containing 0.1% bovine serum albumin are added to each well and the plates are sealed and shaken for ca. 2 hours before being read on an IGEN instrument.

TNFα ELISA Assay

Human TNFα can be assayed using a commercial assay kit (AMS Biotechnology, 211-90-164-40) according to the manufacturers' instructions but with TNFα calibration curves prepared using Pharmingen TNFα (cat No. 555212).

***In Vivo* Biological Assays**

The *in vitro* enzymatic PDE4B inhibition assay(s) described above or generally similar assays should be regarded as being the primary test(s) of biological activity. However, some additional *in vivo* biological tests, which are optional and which are not an essential measure of either efficacy or side-effects, and which have not necessarily been carried out, are described below.

In Vivo Assay 1. LPS-induced pulmonary neutrophilia in rats: effect of orally administered PDE4 inhibitors

Pulmonary neutrophil influx has been shown to be a significant component to the family of pulmonary diseases like chronic obstructive pulmonary disease (COPD) which can involve chronic bronchitis and/or emphysema (G.F. Filley, *Chest.* 2000; 117(5); 251s-260s). The purpose of this neutrophilia model is to study the potentially anti-inflammatory effects *in vivo* of orally administered PDE4 inhibitors on neutrophilia induced by inhalation of aerosolized lipopolysaccharide (LPS), modelling the neutrophil inflammatory component(s) of COPD. See the literature section below for scientific background.

Male Lewis rats (Charles River, Raleigh, NC, USA) weighing approximately 300-400 grams are pretreated with either (a) test compound, for example suspended in ca. 0.5% methylcellulose (obtainable from Sigma-Aldrich, St Louis, MO, USA) in water or (b) vehicle only, delivered orally in a dose volume of ca. 10 ml/kg. Generally, dose response curves can for example be generated using the following approx. doses of PDE4 inhibitors: 2.0, 0.4, 0.08, 0.016 and 0.0032 mg/kg. About thirty minutes following pretreatment, the rats are exposed to aerosolized LPS (Serotype E. Coli 026:B6 prepared by trichloroacetic acid extraction, obtainable from Sigma-Aldrich, St Louis, MO, USA), generated from a nebulizer containing a ca. 100 μg/ml LPS solution (ca. 100 ug/ml). Rats are exposed to the LPS aerosol at a rate of ca. 4 L/min for ca. 20 minutes. LPS exposure is carried out in a closed chamber with internal dimensions of roughly 45 cm length x 24 cm width x 20 cm height. The nebulizer and exposure chamber are contained in a certified fume hood. At about 4 hours-post LPS exposure the rats are euthanized by overdose with pentobarbital at ca. 90 mg/kg, administered intraperitoneally. Bronchoalveolar lavage (BAL) is performed through a 14 gauge blunt needle into the exposed trachea. Five, 5 ml washes are performed to collect a total of 25 ml of BAL fluid. Total cell counts and leukocyte differentials are performed on BAL fluid in order to calculate neutrophil influx into the lung. Percent neutrophil inhibition at each dose (cf. vehicle) is calculated and a variable slope, sigmoidal dose-response curve is generated, usually using Prism Graph-Pad. The dose-response curve is used to calculate an ED50 value (in mg per kg of body weight) for inhibition by the PDE4 inhibitor of the LPS-induced neutrophilia.

Alternative method: In an alternative simpler embodiment of the procedure, a single oral dose of 10 mg/kg, or more usually 1.0 mg/kg or 0.3 mg/kg, of the PDE4 inhibitor (or vehicle) is administered to the rats, and percent neutrophil inhibition is calculated and reported for that specific dose.

Literature:

Filley G.F. Comparison of the structural and inflammatory features of COPD and asthma. *Chest.* 2000; 117(5) 251s-260s.

Howell RE, Jenkins LP, Fielding LE, and Grimes D. Inhibition of antigen-induced pulmonary eosinophilia and neutrophilia by selective inhibitors of phosphodiesterase types 3 and 4 in brown Norway rats. *Pulmonary Pharmacology.* 1995; 8: 83-89.

Spond J, Chapman R, Fine J, Jones H, Kreutner W, Kung TT, Minnicozzi M. Comparison of PDE 4 inhibitors, Rolipram and SB 207499 (Ariflo™), in a rat model of pulmonary neutrophilia. *Pulmonary Pharmacology and Therapeutics.* 2001; 14: 157-164.

Underwood DC, Osborn RR, Bochnowicz S, Webb EF, Rieman DJ, Lee JC, Romanic AM, Adams JL, Hay DWP, and Griswold DE. SB 239063, a p38 MAPK inhibitor, reduces neutrophilia, inflammatory cytokines, MMP-9, and fibrosis in lung. *Am J Physiol Lung Cell Mol Physiol.* 2000; 279: L895-L902.

In Vivo Assay 2. Rat Pica Model of emesis

Background: Selective PDE4 inhibitors have been shown to inhibit inflammation in various *in vitro* and *in vivo* models by increasing intracellular levels of cAMP of many immune cells (e.g. lymphocytes, monocytes). However, a side effect of some PDE4 inhibitors in some species is emesis. Because many rat models of inflammation are well characterized, they can be used in procedures (see e.g. In Vivo Assay 1 above) to show beneficial anti-inflammatory effects of PDE 4 inhibitors. However rats have no emetic response (they have no vomit reflex), so that the relationship between beneficial anti-inflammatory effects of PDE 4 inhibitors and emesis is difficult to study directly in rats.

However, in 1991, Takeda *et al.* (see Literature section below) demonstrated that the pica feeding response is analogous to emesis in rats. Pica feeding is a behavioural response to illness in rats wherein rats eat non-nutritive substances such as earth or in particular clay (e.g. kaolin) which may help to absorb toxins. Pica feeding can be induced by motion and chemicals (especially chemicals which are emetic in humans), and can be inhibited pharmacologically with drugs that inhibit emesis in humans. The Rat Pica Model, In Vivo Assay 2, can determine the level of pica response of rats to PDE 4 inhibition at pharmacologically relevant doses in parallel to *in vivo* anti-inflammatory Assays in (a separate set of) rats (e.g. In Vivo Assay 1 above).

Anti-inflammatory and pica assays in the same species together can provide data on the "therapeutic index" (TI) in the rat of the compounds/salts of the invention. The Rat TI can for example be calculated as the ratio of a) the potentially-emetic Pica Response ED50 dose from Assay 2 to b) the rat anti-inflammatory ED50 dose (e.g. measured by rat neutrophilia-inhibition in eg In Vivo Assay 1), with larger TI ratios possibly indicating lower emesis at many anti-inflammatory doses. This might allow a choice of a non-emetic or low-emetic pharmaceutical dose of the compounds or salts of the invention which has an anti-inflammatory effect. It is recognised however that achieving a low-emetic PDE4 inhibitory compound is not essential to the invention.

Procedure: On the first day of the experiment, the rats are housed individually in cages without bedding or "enrichment". The rats are kept off of the cage floor by a wire screen. Pre-weighed food cups containing standard rat chow and clay pellets are placed in the cage. The clay pellets, obtainable from Languna Clay Co, City of Industry,

CA, USA, are the same size and shape as the food pellets. The rats are acclimated to the clay for 72 hours, during which time the cups and food and clay debris from the cage are weighed daily on an electronic balance capable of measuring to the nearest 0.1 grams. By the end of the 72 hour acclimation period the rats generally show no interest in the clay pellets.

At the end of 72 hours the rats are placed in clean cages and the food cups weighed. Rats that are still consuming clay regularly are removed from the study. Immediately prior to the dark cycle (the time when the animals are active and should be eating) the animals are split into treatment groups and dosed orally with a dose of the compound/salt of the invention (different doses for different treatment groups) or with vehicle alone, at a dose volume of ca. 2 ml/kg. In this oral dosing, the compound/salt can for example be in the form of a suspension in ca. 0.5% methylcellulose (obtainable Sigma-Aldrich, St. Louis, MO, USA) in water. The food and clay cups and cage debris are weighed the following day and the total clay and food consumed that night by each individual animal is calculated.

A dose response is calculated by first converting the data into quantal response, where animals are either positive or negative for the pica response. A rat is "pica positive" if it consumes greater than or equal to 0.3 grams of clay over the mean of its control group. The D50 value is usually calculated using logistic regression performed by the Statistica software statistical package. A Pica Response ED50 value in mg per kg of body weight can then be calculated.

The Pica Response ED50 value can be compared to the neutrophilia-inhibition ED50 values for the same compound administered orally to the rat (measurable by In Vivo Assay 1 above), so that a Therapeutic Index (TI) in rats can be calculated thus:

$$\text{Rat Therapeutic index (TI) (50/50)} = \frac{\text{Pica Response ED50 value}}{\text{rat neutrophilia-inhibition ED50 value}}$$

In general, the Therapeutic Index (TI) calculated this way is often substantially different to, and for example can often be substantially higher than, the TI (D20/D50) calculated in the ferret (see In vivo Assay 4 below).

Alternatively, e.g. for a simpler test, the In Vivo Assay 2 (pica) can use only a single oral dose of the test compound (e.g. 10 mg/kg orally).

Literature:

Beavo JA, Contini, M., Heaslip, R.J. Multiple cyclic nucleotide phosphodiesterases. *Mol Pharmacol.* 1994; 46:399-405.

Spond J, Chapman R, Fine J, Jones H, Kreutner W, Kung TT, Minnicozzi M. Comparison of PDE 4 inhibitors, Rolipram and SB 207499 (Ariflo™), in a rat model of pulmonary neutrophilia. *Pulmonary Pharmacology and Therapeudtics.* 2001; 14:157-164.

Takeda N, Hasegawa S, Morita M, and Matsunaga T. Pica in rats is analogous to emesis: an animal model in emesis research. *Pharmacology, Biochemistry and Behavior.* 1991; 45:817-821.

Takeda N, Hasegawa S, Morita M, Horii A, Uno A, Yamatodani A and Matsunaga T. Neuropharmacological mechanisms of emesis. I . Effects of antiemetic drugs on motion- and apomorphine-induced pica in rats. *Meth Find Exp Clin Pharmacol.* 1995; 17(9) 589-596.

Takeda N, Hasegawa S, Morita M, Horii A, Uno A, Yamatodani A and Matsunaga T. Neuropharmacological mechanisms of emesis. II . Effects of antiemetic drugs on cisplatin-induced pica in rats. *Meth Find Exp Clin Pharmacol.* 1995; 17(9) 647-652.

In Vivo Assay 3. LPS induced pulmonary neutrophilia in rats: effect of intratracheally administered PDE4 inhibitors

This assay is an animal model of inflammation in the lung – specifically neutrophilia induced by lipopolysaccharide (LPS) – and allows the study of putative inhibition of such neutrophilia (anti-inflammatory effect) by intratracheally (i.t.) administered PDE4 inhibitors. The PDE4 inhibitors are preferably in dry powder or wet suspension form. I.t. administration is one model of inhaled administration, allowing topical delivery to the lung.

Animals: Male CD (Sprague Dawley Derived) rats supplied by Charles River, Raleigh, NC, USA or Charles River, United Kingdom are housed in groups of 5 rats per cage, acclimatised after delivery for at least 5 days with bedding/nesting material regularly changed, fed on SDS diet R1 pelleted food given *ad lib,* and supplied with daily-changed pasteurised animal grade drinking water.

Device for dry powder administration: Disposable 3-way tap between dosing needle and syringe. The intratracheal dosing device (a 3-way sterile tap, Vycon 876.00; or Penn Century dry powder insufflator, DP-4) is weighed, the drug blend or inhalation grade lactose (vehicle control) is then added to the tap, the tap is closed to prevent loss of drug, and the tap is re-weighed to determine the weight of drug in the tap. After dosing, the tap is weighed again to determine the weight of drug that had left the tap. The needle, a Sigma Z21934-7 syringe needle 19-gauge 152 mm (6 inches) long with luer hub, is cut by engineering to approximately 132 mm (5.2 inches), a blunt end is made to prevent them damaging the rat's trachea, and the needle is weighed prior to and after drug delivery to confirm that no drug is retained in the needles after dosing.

Device for wet suspension administration: This is the similar to the above but a blunt dosing needle, whose forward end was slightly angled to the needle axis, is used, with a flexible plastic portex canula inserted into the needle.

Drugs and Materials: Lipopolysaccharide (LPS) (Serotype:0127:B8) (e.g. L3129 Lot 61K4075) is dissolved in phosphate-buffered saline (PBS). PDE4 inhibitors are preferably used in size-reduced (e.g. micronised) form, for example according to the Micronisation Example(s) given above.

For dry powder administration of the drug, the Dry Powder Formulation Example given above, comprising drug and inhalation-grade lactose, can optionally be used. One suitable inhalation-grade lactose that can be used (e.g. Lot E98L4675 Batch 845120) has 10% fines (10% of material under 15um (15 micron) particle size measured by Malvern particle size).

Wet suspensions of the drug (aqueous) can be prepared by adding the required volume of vehicle to the drug; the vehicle used can for example be saline alone or a

mixture of saline/tween (e.g. 0.2% tween 80). The wet suspension is usually sonicated for ca. 10 minutes prior to use.

Preparation, and dosing with PDE 4 inhibitor: Rats are anaesthetised by placing the animals in a sealed Perspex chamber and exposing them to a gaseous mixture of isoflourane (4.5 %), nitrous oxide (3 litres.minute^{-1}) and oxygen (1 litre.minute^{-1}). Once anaesthetised, the animals are placed onto a stainless steel i.t. dosing support table. They are positioned on their back at approximately a 35° angle. A light is angled against the outside of the throat to highlight the trachea. The mouth is opened and the opening of the upper airway visualised. The procedure varies for wet suspension and dry powder administration of PDE4 inhibitors as follows:

Dosing with a Wet suspension: A portex cannula is introduced via a blunt metal dosing needle that has been carefully inserted into the rat trachea. The animals are intratracheally dosed with vehicle or PDE4 inhibitor via the dosing needle with a new internal canula used for each different drug group. The formulation is slowly (ca. 10 seconds) dosed into the trachea using a syringe attached to the dosing needle.

Dosing with a Dry Powder: The The intratracheal dosing device (a three-way sterile tap device, Vycon 876.00; or Penn Century dry powder insufflator, DP-4) and needle are inserted into the rat trachea up to a pre-determined point established to be located approximately 1 cm above the primary bifurcation. Another operator holds the needle at the specified position whilst 2 x 4ml of air (using 3-way tap device) is delivered through the three-way tap by depressing the syringes (ideally coinciding with the animal inspiring), aiming to expel the entire drug quantity from the tap. (Alternatively, 2 x 3ml of air is delevered using Penn Century dry powder insufflator device.) After dosing, the needle and tap or device are removed from the airway, and the tap closed off to prevent any retained drug leaving the tap.

After dosing with either wet suspension or dry powder, the animals are then removed from the table and observed constantly until they have recovered from the effects of anaesthesia. The animals are returned to the holding cages and given free access to food and water; they are observed and any unusual behavioural changes noted.

Exposure to LPS: About 2 hours after i.t. dosing with vehicle control or the PDE4 inhibitor, the rats are placed into sealed Perspex containers and exposed to an aerosol of LPS (nebuliser concentration ca. 150 $\mu g.ml^{-1}$ = ca. 150 ug/ml) for ca. 15 minutes. Aerosols of LPS are generated by a nebuliser (DeVilbiss, USA) and this is directed into the Perspex exposure chamber. Following the 15-minute LPS-exposure period, the animals are returned to the holding cages and allowed free access to both food and water.

[In an alternative embodiment, the rats can be exposed to LPS less than 2 hours (e.g. about 30 minutes) after i.t. dosing. In another alternative embodiment, the rats can be exposed to LPS more than 2 hours (e.g. ca. 4 to ca. 24 hours) after i.t. dosing by vehicle or PDE4 inhibitor, to test whether or not the PDE4 inhibitor has a long duration of action (which is not essential).]

Bronchoalveolar lavage: About 4 hours after LPS exposure the animals are killed by overdose of sodium pentobarbitone (i.p.). The trachea is cannulated with polypropylene tubing and the lungs are lavaged (washed out) with 3 x 5 mls of heparinised (25 units.ml^{-1}) phosphate buffered saline (PBS).

Neutrophil cell counts: The Bronchoalveolar lavage (BAL) samples are centrifuged at ca. 1300 rpm for ca. 7 minutes. The supernatant is removed and the resulting cell pellet resuspended in ca. 1 ml PBS. A cell slide of the resuspension fluid is prepared by placing ca. 100µl (ca. 100ul) of resuspended BAL fluid into cytospin holders and then is spun at ca. 5000 rpm for ca. 5 minutes. The slides are allowed to air dry and then stained with Leishmans stain (ca. 20 minutes) to allow differential cell counting. The total cells are also counted from the resuspension. From these two counts, the total numbers of neutrophils in the BAL are determined. For a measure of PDE4-inhibitor-induced inhibition of neutrophilia, a comparison of the neutrophil count in rats treated with vehicle and rats treated with PDE4 inhibitors is conducted.

By varying the dose of the PDE4 inhibitor used in the dosing step (e.g. 0.2 or 0.1 mg of PDE4 inhibitor per kg of body weight, down to e.g. 0.01 mg/kg), a dose-response curve can be generated.

In Vivo Assay 4. Evaluation of Therapeutic Index of Orally-administered PDE 4 inhibitors in the conscious ferret

1.1 Materials

The following materials can be used for these studies:

PDE4 inhibitors are prepared for oral (p.o.) administration by dissolving in a fixed volume (ca. 1 ml) of acetone and then adding cremophor to ca. 20% of the final volume. Acetone is evaporated by directing a flow of nitrogen gas onto the solution. Once the acetone is removed, the solution is made up to final volume with distilled water.

LPS is dissolved in phosphate buffered saline.

1.2 Animals

Male ferrets (Mustela Pulorius Furo, weighing 1 – 2 kg) are transported and allowed to acclimatise for not less than 7 days. The diet comprises SDS diet C pelleted food given *ad lib* with Whiskers^{TM} cat food given 3 times per week. The animals are supplied with pasteurised animal grade drinking water changed daily.

1.3 Experimental Protocol(s)

1.3.1 Dosing with PDE4 inhibitors

PDE4 inhibitors are administered orally (p.o.), using a dose volume of ca. 1ml/kg. Ferrets are fasted overnight but allowed free access to water. The animals are orally dosed with vehicle or PDE 4 inhibitor using a ca. 15cm dosing needle that is passed down the back of the throat into the oesophagus. After dosing, the animals are returned to holding cages fitted with perspex doors to allow observation, and given free access to water. The animals are constantly observed and any emetic episodes (retching and vomiting) or behavioural changes are recorded. The animals are allowed access to food ca. 60 – 90 minutes after p.o. dosing.

1.3.2 Exposure to LPS

About thirty minutes after oral dosing with compound or vehicle control, the ferrets are placed into sealed perspex containers and exposed to an aerosol of LPS (ca. 30 μg/ml = ca. 30 ug/ml) for ca. 10 minutes. Aerosols of LPS are generated by a nebuliser (DeVilbiss, USA) and this is directed into the perspex exposure chamber. Following a 10-minute exposure period, the animals are returned to the holding cages and allowed free access to water, and at a later stage, food. General observation of the animals continues for a period of at least 2.5 hours post oral dosing. All emetic episodes and behavioural changes are recorded.

1.3.3 Bronchoalveolar lavage and cell counts

About six hours after LPS exposure the animals are killed by overdose of sodium pentobarbitone administered intraperitoneally. The trachea is then cannulated with polypropylene tubing and the lungs lavaged twice with ca. 20 ml heparinised (10 units/ml) phosphate buffered saline (PBS). The bronchoalveolar lavage (BAL) samples are centrifuged at ca. 1300 rpm for ca. 7 minutes. The supernatant is removed and the resulting cell pellet re-suspended in ca. 1 ml PBS. A cell smear of re-suspended fluid is prepared and stained with Leishmans stain to allow differential cell counting. A total cell count is made using the remaining re-suspended sample. From this, the total number of neutrophils in the BAL sample is determined.

1.3.4 Pharmacodynamic readouts

The following parameters are recorded:

a) % inhibition of LPS-induced pulmonary neutrophilia to determine the dose of PDE4 inhibitor which gives 50% inhibition (D50).

b) Emetic episodes – the number of vomits and retches are counted to determine the dose of PDE4 inhibitor that gives a 20% incidence of emesis (D20).

c) A therapeutic index (TI), using this assay, is then calculated for each PDE4 inhibitor using the following equation:

$$\text{Ferret Therapeutic index (TI) (D20/D50)} = \frac{\text{D20 incidence of emesis in ferret}}{\text{D50 inhibition of neutrophilia in ferret}}$$

It is noted that the Ferret Therapeutic index (TI) (D20/D50) calculated using this in vivo Assay 4 is often substantially different to, and for example is often substantially lower than, the Rat TI (50/50) calculated using the rat oral inflammation and pica feeding Assays 1+2.

The calculation of Ferret TI using the known PDE4 inhibitor roflumilast in this Assay 4 is approximately as follows:

D20 for emesis = about 0.46 mg/kg p.o.,

D50 for ferret neutroplilia = about 0.42 mg/kg p.o.,

Ferret TI = about 1.1.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

EXAMPLES

The various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

In this section, "Intermediates" can represent syntheses of intermediate compounds intended for use in the synthesis of one or more of the "Examples", or "Intermediates" can represent syntheses of intermediate compounds which can be used in the synthesis of compounds of formula (I) or salts thereof. "Examples" are generally exemplary compounds or salts of the invention, for example compounds of formula (I) or (IB) or salts thereof.

Abbreviations used herein:

AcOH	acetic acid
Ac_2O	acetic anhydride
BEMP	2-t-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphazine
BOC_2O	di tert-butyl carbonate
DMSO	dimethyl sulfoxide
DCM	dichloromethane
DMF	dimethyl formamide
DIPEA	diisopropylethyl amine ($^iPr_2NEt$)
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
Et_2O	diethyl ether
Et_3N	triethylamine
EtOH	ethanol
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBT	hydroxybenzotriazole = 1-hydroxybenzotriazole
Lawesson's reagent	2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide
MeCN	acetonitrile
MeOH	methanol
THF	Tetrahydrofuran
HPLC	high pressure liquid chromatography
SPE	solid phase extraction
NMR	nuclear magnetic resonance (in which: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, H = no. of protons)

LCMS	liquid chromatography/mass spectroscopy
TLC	thin layer chromatography
h	hours
T_{RET}	retention time (from LCMS)
Room temperature	this is usually in the range of about 20 to about 25 °C.

General Experimental Details

Machine Methods used herein:

LCMS (liquid chromatography/mass spectroscopy)
Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.
UV wavelength : 215-330nM
Column : 3.3cm x 4.6mm ID, 3μm ABZ+PLUS
Flow Rate : 3ml/min
Injection Volume : 5μl
Solvent A : 95% acetonitrile + 0.05% formic acid
Solvent B : 0.1% formic acid + 10mMolar ammonium acetate
Gradient : 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min
It should be noted that retention times (T_{RET}) quoted herein may vary slightly (+/- 0.1min.) when samples were run on different Waters machines, even though the same type of column and identical flow rates, injection volumes, solvents and gradients were used.
Mass directed autoprep HPLC
The prep column used was a Supelcosil ABZplus (10cm x 2.12cm)
(usually 10cm x 2.12cm x 5 μm).
UV wavelength : 200-320nM
Flow : 20ml/min
Injection Volume: 1ml; or more preferably 0.5 ml
Solvent A : 0.1% formic acid
Solvent B : 95% acetonitrile + 5% formic acid; or more usually 99.95% acetonitrile + 0.05% formic acid
Gradient : 100% A/1min, 100-80% A/9min, 80-1% A/3.5min, 1% A/1.4min, 1-100%A/0.1min

Chiral Columns for Chromatographic Purification

ChiralPak AD, ChiralCel OD and ChiralCel OJ columns can be obtained from:
Chiral Technologies Europe Sarl, Illkirch, France (Telephone: +33 (0)388795200; (cte@chiral.fr; www.chiral.fr).

Whelk-01 columns can be purchased from: Hichrom, 1, The Markham Centre, Station Road, Theale, Reading, Berks. RG7.4PE, United Kingdom (Telephone: +44 (0)1189303660; (info@hichrom.co.uk; www.hichrom.co.uk). Hichrom are agents for the manufacturers Regis Technologies Inc., 8210 Austin Avenue, Morton Grove, IL60053, USA; telephone: +1-847-967-6000; www.registech.com.

Intermediates and Examples

Reagents not detailed in the text below are usually commercially available from chemicals suppliers, e.g. established suppliers such as Sigma-Aldrich. The addresses and/or contact details of the suppliers for some of the starting materials mentioned in the Intermediates and Examples below or the Assays above, or suppliers of chemicals in general, are as follows:

- AB Chem, Inc., 547 Davignon, Dollard-des-Ormeaux, Quebec, H9B 1Y4, Canada
- ABCR GmbH & CO. KG, P.O. Box 21 01 35, 76151 Karlsruhe, Germany
- ACB Blocks Ltd; Kolokolnikov Per, 9/10 Building 2, Moscow, 103045, Russia
- Aceto Color Intermediates (catalogue name), Aceto Corporation, One Hollow Lane, Lake Success, NY, 11042-1215, USA
- Acros Organics, A Division of Fisher Scientific Company, 500 American Road, Morris Plains, NJ 07950, USA
- Apin Chemicals Ltd., 82 C Milton Park, Abingdon, Oxon OX14 4RY, United Kingdom
- Apollo Scientific Ltd., Unit 1A, Bingswood Industrial Estate, Whaley Bridge, Derbyshire SK23 7LY, United Kingdom
- Aldrich (catalogue name), Sigma-Aldrich Company Ltd., Dorset, United Kingdom, telephone: +44 1202 733114; Fax: +44 1202 715460; ukcustsv@eurnotes.sial.com; or
- Aldrich (catalogue name), Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178-9916, USA; telephone: +1-314-771-5765; fax: +1-314-771-5757; custserv@sial.com; or
- Aldrich (catalogue name), Sigma-Aldrich Chemie GmbH, Munich, Germany; telephone: +49 89 6513 0; Fax: +49 89 6513 1169; deorders@eurnotes.sial.com.
- Alfa Aesar, A Johnson Matthey Company, 30 Bond Street, Ward Hill, MA 01835-8099, USA
- Amersham Biosciences UK Ltd, Pollards Wood, Chalfont St Giles, Buckinghamshire HP8 4SP, United Kingdom
– Arch Corporation, 100 Jersey Avenue, Building D, New Brunswick, NJ08901, USA
- Array Biopharma Inc., 1885 33rd Street, Boulder, CO 80301, USA
- AstaTech, Inc., 8301 Torresdale Ave., 19C, Philadelphia, PA 19136, USA
- Austin Chemical Company, Inc., 1565 Barclay Blvd., Buffalo Grove, IL 60089, USA
- Avocado Research, Shore Road, Port of Heysham Industrial Park, Heysham, Lancashire LA3 2XY, United Kingdom
- Bayer AG, Business Group Basic and Fine Chemicals, D-51368 Leverkusen, Germany
- Berk Univar plc, Berk House, P.O.Box 56, Basing View, Basingstoke, Hants RG21 2E6, United Kingdom
- Bionet Research Ltd; Highfield Industrial Estate, Camelford, Cornwall PL32 9QZ UK

- Butt Park Ltd., Braysdown Works, Peasedown St. John, Bath BA2 8LL, United Kingdom
- Chemical Building Blocks (catalogue name), Ambinter, 46 quai Louis Bleriot, Paris, F-75016, France
- ChemBridge Europe, 4 Clark's Hill Rise, Hampton Wood, Evesham, Worcestershire WR11 6FW, United Kingdom
- ChemService Inc., P.O.Box 3108, West Chester, PA 19381, USA
- CiventiChem, PO Box 12041, Research Triangle Park, NC 27709, USA
- Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126, USA
- Dynamit Nobel GmbH, Germany; also available from: Saville Whittle Ltd (UK agents of Dynamit Nobel), Vickers Street, Manchester M40 8EF, United Kingdom
- E. Merck, Germany; or E. Merck (Merck Ltd), Hunter Boulevard, Magna Park, Lutterworth, Leicestershire LE17 4XN, United Kingdom
- Esprit Chemical Company, Esprit Plaza, 7680 Matoaka Road, Sarasota, FL 34243, USA
- Exploratory Library (catalogue name), Ambinter, 46 quai Louis Bleriot, Paris, F-75016, France
- Fluka Chemie AG, Industriestrasse 25, P.O. Box 260, CH-9471 Buchs, Switzerland
- Fluorochem Ltd., Wesley Street, Old Glossop, Derbyshire SK13 7RY, United Kingdom
- Heterocyclic Compounds Catalog (Florida Center for Heterocyclic Compounds, University of Florida, PO Box 117200, Gainsville, FL 32611-7200 USA
- ICN Biomedicals, Inc., 3300 Hyland Avenue, Costa Mesa, CA 92626, USA
- Interchim Intermediates (catalogue name), Interchim, 213 Avenue Kennedy, BP 1140, Montlucon, Cedex, 03103, France
- Key Organics Ltd., 3, Highfield Indusrial Estate, Camelford, Cornwall PL32 9QZ, United Kingdom
- Lancaster Synthesis Ltd., Newgate, White Lund, Morecambe, Lancashire LA3 3DY, United Kingdom
- Manchester Organics Ltd., Unit 2, Ashville Industrial Estate, Sutton Weaver, Runcorn, Cheshire WA7 3PF, United Kingdom
- Matrix Scientific, P.O. Box 25067, Columbia, SC 29224-5067, USA
- Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall PL34 0HW, United Kingdom
- Maybridge Combichem (catalogue name), Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall PL34 0HW, United Kingdom
- Maybridge Reactive Intermediates (catalogue name), Maybridge Chemical Company Ltd., Trevillett, Tintagel, Cornwall PL34 0HW, United Kingdom
- MicroChemistry Building Blocks (catalogue name), MicroChemistry-RadaPharma, Shosse Entusiastov 56, Moscow, 111123, Russia
- Miteni S.p.A., Via Mecenate 90, Milano, 20138, Italy
- Molecular Devices Corporation, Sunnydale, CA, USA
- N.D. Zelinsky Institute, Organic Chemistry, Leninsky prospect 47, 117913 Moscow B-334, Russia
- Oakwood Products Inc., 1741, Old Dunbar Road, West Columbia, SC, 29172, USA
- OmegaChem Inc., 8800, Boulevard de la Rive Sud, Levis, PQ, G6V 9H1, Canada
- Optimer Building Block (catalogue name), Array BioPharma, 3200 Walnut Street, Boulder, CO 80301, USA

- Peakdale Molecular Ltd., Peakdale Science Park, Sheffield Road, Chapel-en-le-Frith, High Peak SK23 0PG, United Kingdom
- Pfaltz & Bauer, Inc., 172 East Aurora Street, Waterbury, CT 06708, USA
- Rare Chemicals (catalogue name), Rare Chemicals GmbH, Schulstrasse 6, 24214 Gettorf, Germany
- SALOR (catalogue name) (Sigma Aldrich Library of Rare Chemicals), Aldrich Chemical Company Inc, 1001 West Saint Paul Avenue, Milwaukee, WI 53233, USA
- Sigma (catalogue name), Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178-9916, USA; see "Aldrich" above for other non-US addresses and other contact details
- SIGMA-RBI, One Strathmore Road, Natick, MA 01760-1312, USA
- Synchem OHG Heinrich-Plett-Strasse 40, Kassel, D-34132, Germany
- Syngene International Pvt Ltd, Hebbagodi, Hosur Road, Bangalore, India.
- TCI America, 9211 North Harborgate Street, Portland, OR 97203, USA
- TimTec Building Blocks A or B, TimTec, Inc., P O Box 8941, Newark, DE 19714-8941, USA
- TimTec Overseas Stock, TimTec Inc., 100 Interchange Blvd. Newark, DE 19711, USA
- TimTec Stock Library, TimTec, Inc., P O Box 8941, Newark, DE 19714-8941, USA
- Trans World Chemicals, Inc., 14674 Southlawn Lane, Rockville, MD 20850, USA
- Ubichem PLC, Mayflower Close, Chandlers Ford Industrial Estate, Eastleigh, Hampshire SO53 4AR, United Kingdom
- Ultrafine (UFC Ltd.), Synergy House, Guildhall Close, Manchester Science Park, Manchester M15 6SY, United Kingdom

Table of Intermediates

Inter-mediate Number	Name
1	Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
2	4-Aminotetrahydropyran
3	1-Acetyl-4-aminopiperidine
4	Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
5	ethyl 4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
6	Ethyl 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
7	Ethyl 1-ethyl-4-[(4-hydroxycyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
8	Ethyl 1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
9	Ethyl 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
10	Ethyl 4-chloro-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate

11	Ethyl 1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
12	Ethyl 1-ethyl-4-{[(1*SR*,3*RS*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
13	1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
14	4-(Cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
15	4-[(1-Acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
16	1-Ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
17	1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
18	1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
19	1-Ethyl-4-{[(1*SR*,3*RS*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
20	*N*-[(1*E*)-(2,4-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide
21	2-methyl-*N*-[(1*E*)-(2-methylphenyl)methylidene]-2-propanesulfinamide
22	*N*-[(1*E*)-(3-hydroxyphenyl)methylidene]-2-methyl-2-propanesulfinamide
23	2-methyl-*N*-{(1*E*)-[3-(methyloxy)phenyl]methylidene}-2-propanesulfinamide
24	2-methyl-*N*-{(1*E*)-[4-(methyloxy)phenyl]methylidene}-2-propanesulfinamide
25	*N*-[(1*E*)-(4-bromophenyl)methylidene]-2-methyl-2-propanesulfinamide
26	2-methyl-*N*-[(1*E*)-(4-methylphenyl)methylidene]-2-propanesulfinamide
27	*N*-{(1*E*)-[4-(ethyloxy)phenyl]methylidene}-2-methyl-2-propanesulfinamide
28	2-methyl-*N*-{(1*E*)-[4-(propyloxy)phenyl]methylidene}-2-propanesulfinamide
29	*N*-((1*E*)-{4-[(difluoromethyl)oxy]phenyl}methylidene)-2-methyl-2-propanesulfinamide
30	2-methyl-*N*-{(1*E*)-[4-(trifluoromethyl)phenyl]methylidene}-2-propanesulfinamide
31	2-methyl-*N*-{(1*E*)-[4-(1-methylethyl)phenyl]methylidene}-2-propanesulfinamide
32	*N*-[(1*E*)-(2,3-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide
33	*N*-[(1*E*)-(4-chloro-2-fluorophenyl)methylidene]-2-methyl-2-propanesulfinamide
34	*N*-[(1*E*)-(3,4-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide
35	*N*-[(1*E*)-(3,5-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide
36	N-[(1E)-(3-chloro-4-methylphenyl)methylidene]-2-methyl-2-propanesulfinamide
37	*N*-[1-(2,4-dimethylphenyl)ethyl]-2-methyl-2-propanesulfinamide

38	2-methyl-*N*-[1-(2-methylphenyl)ethyl]-2-propanesulfinamide
39	*N*-{1-[4-(ethyloxy)phenyl]ethyl}-2-methyl-2-propanesulfinamide
40	*N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-2-methyl-2-propanesulfinamide
41	2-methyl-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-2-propanesulfinamide
42	*N*-[1-(2,3-dimethylphenyl)ethyl]-2-methyl-2-propanesulfinamide
43	*N*-[1-(4-chloro-2-fluorophenyl)ethyl]-2-methyl-2-propanesulfinamide
44	*N*-[1-(3-chloro-4-methylphenyl)ethyl]-2-methyl-2-propanesulfinamide
45	2-methyl-*N*-[1-(2-methylphenyl)propyl]-2-propanesulfinamide
46	*N*-[1-(3-hydroxyphenyl)propyl]-2-methyl-2-propanesulfinamide
47	2-methyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-2-propanesulfinamide
48	2-methyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-2-propanesulfinamide
49	*N*-[1-(4-bromophenyl)propyl]-2-methyl-2-propanesulfinamide
50	2-methyl-*N*-[1-(4-methylphenyl)propyl]-2-propanesulfinamide
50a	2-methyl-*N*-[(1*S*)-1-(4-methylphenyl)propyl]-2-propanesulfinamide
51	*N*-{1-[4-(ethyloxy)phenyl]propyl}-2-methyl-2-propanesulfinamide
52	2-methyl-*N*-{1-[4-(propyloxy)phenyl]propyl}-2-propanesulfinamide
53	*N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-2-methyl-2-propanesulfinamide
54	2-methyl-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-2-propanesulfinamide
55	2-methyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-2-propanesulfinamide
55a	2-methyl-*N*-{(1*S*)-1-[4-(1-methylethyl)phenyl]propyl}-2-propanesulfinamide
56	*N*-[1-(2,3-dimethylphenyl)propyl]-2-methyl-2-propanesulfinamide
57	*N*-[1-(2,4-dimethylphenyl)propyl]-2-methyl-2-propanesulfinamide
58	*N*-[1-(4-chloro-2-fluorophenyl)propyl]-2-methyl-2-propanesulfinamide
58a	*N*-[(1*S*)-1-(4-chloro-2-fluorophenyl)propyl]-2-methyl-2-propanesulfinamide
59	*N*-[1-(3,4-dimethylphenyl)propyl]-2-methyl-2-propanesulfinamide
60	*N*-[1-(3,5-dimethylphenyl)propyl]-2-methyl-2-propanesulfinamide
61	*N*-[1-(3-chloro-4-methylphenyl)propyl]-2-methyl-2-propanesulfinamide
62	[1-(2,4-dimethylphenyl)ethyl]amine hydrochloride
63	[1-(2-methylphenyl)ethyl]amine hydrochloride
64	{1-[4-(ethyloxy)phenyl]ethyl}amine hydrochloride
65	(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)amine hydrochloride
66	{1-[4-(trifluoromethyl)phenyl]ethyl}amine hydrochloride
67	[1-(2,4-dimethylphenyl)ethyl]amine trifluoroacetate
68	[1-(4-chloro-2-fluorophenyl)ethyl]amine hydrochloride
69	[1-(3-chloro-4-methylphenyl)ethyl]amine hydrochloride
70	[1-(2-methylphenyl)propyl]amine hydrochloride
71	3-(1-aminopropyl)phenol hydrochloride
72	{1-[3-(methyloxy)phenyl]propyl}amine hydrochloride
73	{1-[4-(methyloxy)phenyl]propyl}amine hydrochloride
74	[1-(4-bromophenyl)propyl]amine hydrochloride
75	[1-(4-methylphenyl)propyl]amine hydrochloride

75a	[(1R)-(4-methylphenyl)propyl]amine hydrochloride
76	{1-[4-(ethyloxy)phenyl]propyl}amine hydrochloride
77	{1-[4-(propyloxy)phenyl]propyl}amine hydrochloride
78	(1-{4-[(difluoromethyl)oxy]phenyl}propyl)amine hydrochloride
79	{1-[4-(trifluoromethyl)phenyl]propyl}amine hydrochloride
80	{1-[4-(1-methylethyl)phenyl]propyl}amine hydrochloride
80a	{(1R)-[4-(1-methylethyl)phenyl]propyl}amine hydrochloride
81	[1-(2,3-dimethylphenyl)propyl]amine hydrochloride
82	[1-(2,4-dimethylphenyl)propyl]amine hydrochloride
83	[1-(4-chloro-2-fluorophenyl)propyl]amine hydrochloride
83a	[(1R)-(4-chloro-2-fluorophenyl)propyl]amine hydrochloride
84	[1-(3,4-dimethylphenyl)propyl]amine hydrochloride
85	[1-(3,5-dimethylphenyl)propyl]amine hydrochloride
86	[1-(3-chloro-4-methylphenyl)propyl]amine hydrochloride
87	[1-(3,5-dimethylphenyl)ethyl]amine hydrochloride
88	3-(1-aminoethyl)phenol hydrochloride
89	{1-[4-(1-methylethyl)phenyl]ethyl}amine hydrochloride
90	[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]amine hydrochloride
91	[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]amine hydrochloride
92	(2,2,2-trifluoro-1-phenylethyl)amine hydrochloride
93	[1-(4-bromophenyl)-2,2,2-trifluoroethyl]amine hydrochloride
94	{2,2,2-trifluoro-1-[3-(methyloxy)phenyl]ethyl}amine hydrochloride
95	(1-phenylhexyl)amine hydrochloride
96	(1-phenylpentyl)amine hydrochloride
97	[cyclopropyl(phenyl)methyl]amine hydrochloride
98	(2-methyl-1-phenylpropyl)amine hydrochloride
99	(1-phenylbutyl)amine hydrochloride
100	[1-(2,4-dimethylphenyl)ethyl]amine trifluoroacetate
101	[1-(2,4-dimethylphenyl)ethyl]amine trifluoroacetate
102	Ethyl 4-[(1-{[(1,1-dimethylethyl)oxy]carbonyl}-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
103	Ethyl 1-ethyl-4-(4-piperidinylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate hydrochloride
104	Ethyl 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
105	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid
106	4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
107	4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl chloride
108	4-chloro-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
109	4-chloro-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-

carboxamide

110 1,1-dimethylethyl [1-(aminocarbonyl)-4-piperidinyl]carbamate

111 4-amino-1-piperidinecarboxamide hydrochloride

112 1,1-dimethylethyl [4-(aminocarbonyl)cyclohexyl]carbamate

113 4-aminocyclohexanecarboxamide hydrochloride

114 1,1-dimethylethyl [*cis*-4-(aminocarbonyl)cyclohexyl]carbamate

115 1,1-dimethylethyl [*trans*-4-(aminocarbonyl)cyclohexyl]carbamate

116 *cis*-4-aminocyclohexanecarboxamide hydrochloride

117 *trans*-4-aminocyclohexanecarboxamide hydrochloride

118 ethyl 4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate

119 ethyl 4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate

120 4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid

121 4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid

122 4-chloro-*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

123 *N*-[(1*E*)-(2-ethylphenyl)methylidene]-2-methyl-2-propanesulfinamide

124 *N*-[(1*E*)-(4-ethylphenyl)methylidene]-2-methyl-2-propanesulfinamide

125 *N*-[(1*E*)-(2,5-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide

126 *N*-[(1*E*)-(2,6-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide

127 2-methyl-*N*-[(1*E*)-(2,4,6-trimethylphenyl)methylidene]-2-propanesulfinamide

128 *N*-[(1*R*)-1-(2-ethylphenyl)ethyl]-2-methyl-2-propanesulfinamide

129 *N*-[(1*R*)-1-(4-ethylphenyl)ethyl]-2-methyl-2-propanesulfinamide

130 *N*-[(1*R*)-1-(2,5-dimethylphenyl)ethyl]-2-methyl-2-propanesulfinamide

131 2-methyl-*N*-[(1*R*)-1-(2,4,6-trimethylphenyl)ethyl]-2-propanesulfinamide

132 *N*-[(1*S*)-1-(2-ethylphenyl)propyl]-2-methyl-2-propanesulfinamide

133 *N*-[(1*S*)-1-(4-ethylphenyl)propyl]-2-methyl-2-propanesulfinamide

134 *N*-[1-(2,5-dimethylphenyl)propyl]-2-methyl-2-propanesulfinamide

135 *N*-[(1*S*)-1-(2,6-dimethylphenyl)propyl]-2-methyl-2-propanesulfinamide

136 2-methyl-*N*-[(1*S*)-1-(2,4,6-trimethylphenyl)propyl]-2-propanesulfinamide

137 [(1*R*)-1-(2-ethylphenyl)ethyl]amine hydrochloride

138 [(1*R*)-1-(4-ethylphenyl)ethyl]amine hydrochloride

139 [(1*R*)-1-(2,5-dimethylphenyl)ethyl]amine hydrochloride

140 [(1*R*)-1-(2,4,6-trimethylphenyl)ethyl]amine hydrochloride

141 [(1*R*)-1-(2-ethylphenyl)propyl]amine hydrochloride

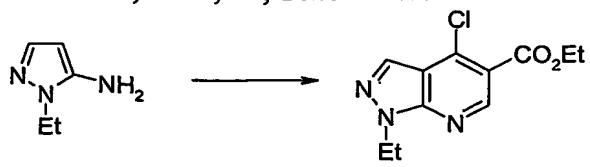
142 [(1*R*)-1-(4-ethylphenyl)propyl]amine hydrochloride

143 [(1*R*)-1-(2,5-dimethylphenyl)propyl]amine hydrochloride

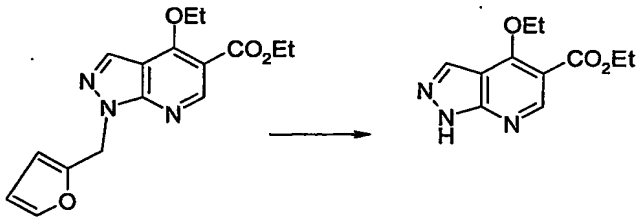
144 [(1*R*)-1-(2,6-dimethylphenyl)propyl]amine hydrochloride

145	[(1*R*)-1-(2,4,6-trimethylphenyl)propyl]amine hydrochloride
146	ethyl 4-[((3S)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-3-pyrrolidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
147	ethyl 4-[((3R)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-3-pyrrolidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
148	ethyl 1-ethyl-4-[(3*S*)-3-pyrrolidinylamino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate hydrochloride
149	ethyl 1-ethyl-4-[(3R)-3-pyrrolidinylamino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate hydrochloride
150	ethyl 4-{[(3*S*)-1-(aminocarbonyl)-3-pyrrolidinyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
151	ethyl 4-{[(3*R*)-1-(aminocarbonyl)-3-pyrrolidinyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
152	4-{[(3*S*)-1-(aminocarbonyl)-3-pyrrolidinyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
153	4-{[(3R)-1-(aminocarbonyl)-3-pyrrolidinyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
154	1,1-dimethylethyl (*cis*-4-{[methyl(methyloxy)amino]carbonyl}cyclohexyl)carbamate
155	1,1-dimethylethyl (*cis*-4-acetylcyclohexyl)carbamate
156	1-(*cis*-4-aminocyclohexyl)ethanone hydrochloride
157	ethyl 4-[(4-acetylcyclohexyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (mixture of *cis* and *trans* isomers)
158	4-[(4-acetylcyclohexyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (mixture of *cis* and *trans* isomers)
159	(RS)-1,1-dimethylethyl [*cis*-4-(1-hydroxyethyl)cyclohexyl]carbamate
160	(RS)-1-(*cis*-4-aminocyclohexyl)ethanol hydrochloride
161	ethyl 1-ethyl-4-{[(1*S*,3*S*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate and ethyl 1-ethyl-4-{[(1R,3R)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate
162	1-ethyl-4-{[(1*R*,3*R*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
163	4-[(1-{[(1,1-dimethylethyl)oxy]carbonyl}-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid
164	1,1-dimethylethyl 4-{[1-ethyl-5-({[(1*R*)-1-(4-methylphenyl)ethyl]amino}carbonyl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl]amino}-1-piperidinecarboxylate
165	1,1-dimethylethyl 4-{[5-({[1-(2,4-dimethylphenyl)propyl]amino}carbonyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl]amino}-1-piperidinecarboxylate
166	4-Amino-4-(3-methylphenyl)butyric acid
167	4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-4-(3-methylphenyl)butanoic acid
168	1,1-dimethylethyl [4-(dimethylamino)-1-(3-methylphenyl)-4-oxobutyl]carbamate
169	4-amino-*N*,*N*-dimethyl-4-(3-methylphenyl)butanamide hydrochloride

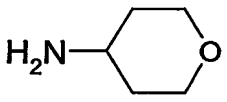
Intermediate 1: Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
This can be prepared from commercially available 5-amino-1-ethyl pyrazole as described by G. Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027:



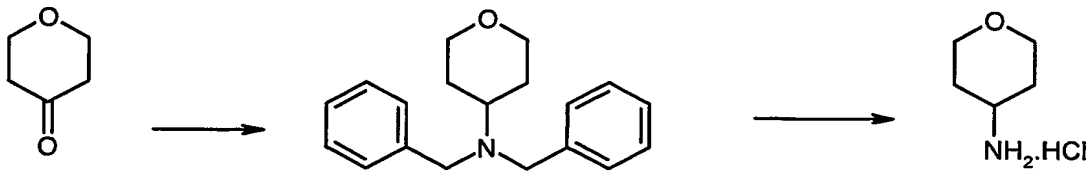
Intermediate 1A: Ethyl 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate
This can be prepared by oxidative cleavage (SeO_2) of 1-furanylmethyl derivative, as described by T. M. Bare *et. al.* In *J. Med. Chem.*, 1989, 32, 2561-2573, (further referenced to Zuleski, F. R., Kirkland, K. R., Melgar, M. D.; Malbica, *J. Drug. Metab. Dispos.*, 1985, 13, 139):



Intermediate 2: 4-Aminotetrahydropyran
Commercially available from Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126, USA (CAS 38041-19-9)



Intermediate 2A: Tetrahydro-2H-pyran-4-amine hydrochloride = 4-Aminotetrahydropyran hydrochloride



Step1: N,N-dibenzyltetrahydro-2H-pyran-4-amine
Dibenzylamine (34.5g) and acetic acid (6.7ml) were added to a stirred solution of tetrahydro-4H-pyran-4-one (16.4g, commercially available from e.g. Aldrich) in dichloromethane (260ml) at 0 °C to 5 °C. After 2.5h at 0 °C to 5 °C, sodium triacetoxyborohydride (38.9g) was added portionwise, and the mixture was allowed to warm to room temperature. After stirring at room temperature overnight, the reaction

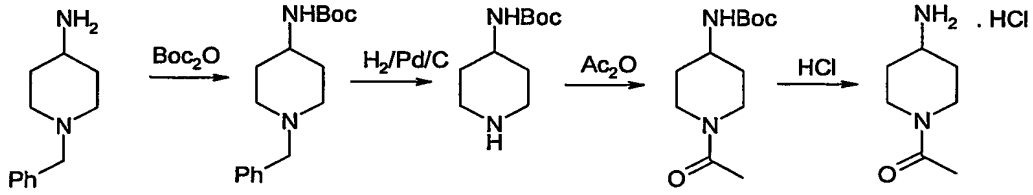
mixture was washed successively with 2M-sodium hydroxide (200ml and 50ml), water (2 x 50ml) and brine (50ml), then dried and evaporated to give a yellow oil (45g). This oil was stirred with methanol (50ml) at 4 °C for 30min to give the product as a white solid (21.5g). LCMS showed $MH^+ = 282$; $T_{RET} = 1.98$ min.

Step 2: Tetrahydro-2H-pyran-4-amine hydrochloride

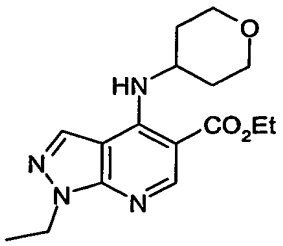
N,N-dibenzyltetrahydro-2*H*-pyran-4-amine (20.5g) was dissolved in ethanol (210ml) and hydrogenated over 10% palladium on carbon catalyst (4g) at 100 psi for 72h at room temperature. The reaction mixture was filtered and the filtrate was adjusted to pH 1 with 2M-hydrogen chloride in diethyl ether. Evaporation of solvents gave a solid which was triturated with diethyl ether to give the product as a white solid (9.23g). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) 8.24 (br. s, 3H), 3.86 (dd, 12, 4Hz, 2H), 3.31 (dt, 2, 12Hz, 2H), 3.20 (m, 1H), 1.84 (m, 2H), 1.55 (dq, 4, 12Hz, 2H).

Intermediate 3: 1-Acetyl-4-aminopiperidine

This can be prepared from commercially available N1-benzyl-4-aminopiperidine as described by Yamada *et. al.* In WO 00/42011:



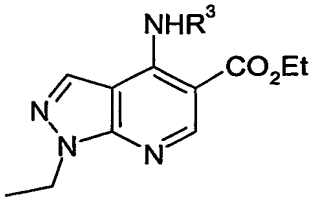
Intermediate 4: Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

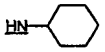
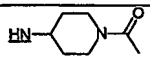


Intermediate 1 (0.20g) and triethylamine (0.55ml) were suspended in ethanol (8ml) and 4-aminotetrahydropyran (Intermediate 2, 0.088g) was added. The mixture was stirred under nitrogen and heated at 80°C for 16h, then concentrated *in vacuo*. The residue was partitioned between DCM and water. The layers were separated and the organic layer was loaded directly onto an SPE cartridge (silica, 5g) which was eluted sequentially with; (i) DCM, (ii) DCM : Et_2O (2:1), (iii) DCM : Et_2O (1:1), (iv) Et_2O and (v) EtOAc. Fractions

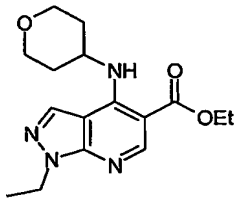
containing desired material were combined and concentrated *in vacuo* to afford Intermediate 4 (0.21g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.93$min.

Similarly prepared from Intermediate 1 were the following:



	NHR^3	Amine reagent	MH^+ ion	T_{RET} (min)
Intermediate 5		Cyclohexylamine	317	3.65
Intermediate 6		Intermediate 3	360	2.71

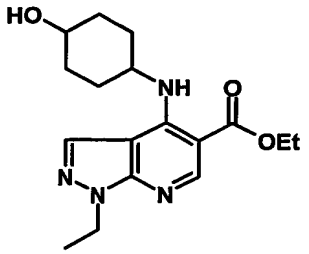
Intermediate 4



Alternative synthesis: Instead of the method shown above Intermediate 4 can also be made using the following Method B:

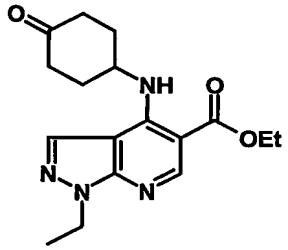
Method B: Intermediate 1 (2.5g) was dissolved in acetonitrile (15ml). 4-Aminotetrahydropyran hydrochloride (Intermediate 2A) (1.1g) and N,N-diisopropylethylamine (9.4ml) were added and the mixture stirred under nitrogen at 85 °C for 16h. A trace of starting material remained, so an additional portion of 4-aminotetrahydropyran hydrochloride (0.11g) was added and stirring continued at 85 °C for a further 16h. The mixture was then concentrated in vacuo. The residue was partitioned between DCM and water. The layers were separated and the organic layer was washed with further water (2x20ml) then dried (Na_2SO_4) and concentrated in vacuo. The residue was further purified by chromatography using Biotage (silica, 90g), eluting with cyclohexane : ethyl acetate to afford Intermediate 4 (2.45g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.90$min.

Intermediate 7: Ethyl 1-ethyl-4-[(4-hydroxycyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



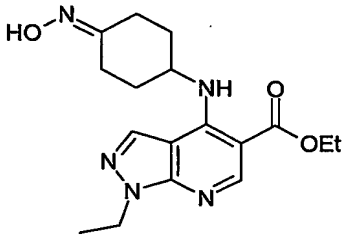
Intermediate 1 (1.5g, 5.9mmol) was dissolved in MeCN (80ml). Trans-4-aminocyclohexanol (0.817g, 7.1mmol, commercially available from TCI-America; alternatively (e.g. as the HCl salt) from Aldrich) and DIPEA (6.18ml, 35.5mmol) were added and the mixture was stirred at 85°C for 16h. The mixture was concentrated *in vacuo*, and the residue was partitioned between DCM (120ml) and water (30ml). The phases were separated and the organic phase was dried (Na_2SO_4) and evaporated to give a pale yellow solid. The solid was dissolved in a mixture of DCM (10ml) and chloroform (3ml), and applied in equal portions to two SPE cartridges (silica, 20g) which were eluted sequentially with a gradient of EtOAc:cyclohexane (1:16, then 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing the desired material were combined and evaporated *in vacuo* to give Intermediate 7 (1.89g) as a white solid. LCMS showed $MH^+ = 333$; $T_{RET} = 2.79$min.

Intermediate 8: Ethyl 1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



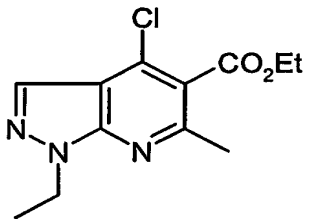
Intermediate 7 (1.893g, 5.7mmol) was suspended in acetone (12ml) and the stirred suspension was treated at 0°C with Jones reagent (1.81ml). After 30min, a further quantity of Jones reagent (1.81ml) was added to the reaction mixture which was maintained at 0°C. After a further 2h, a final portion of Jones reagent (1.44ml) was added to the reaction mixture, and stirring at 0°C was continued for 1h. Isopropanol (3.8ml) was added to the reaction mixture, followed by water (15ml). The resulting mixture was extracted with EtOAc (2 x 40ml). The combined organic extracts were washed with water (8ml), dried (Na_2SO_4) and evaporated to a grey solid. The solid was dissolved in DCM (10ml) and applied in equal portions to two SPE cartridges (silica, 20g) which were eluted sequentially with a gradient of EtOAc:cyclohexane (1:16, then 1:8, 1:4, 1:2, and 1:1). Fractions containing the desired material were combined and evaporated *in vacuo* to give Intermediate 8 (1.893g) as a white solid. LCMS showed $MH^+ = 331$; $T_{RET} = 2.84$min.

Intermediate 9: Ethyl 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



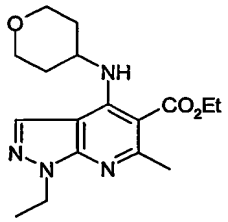
A mixture of Intermediate 8 (200mg), hydroxylamine hydrochloride (50mg) and anhydrous potassium carbonate (420mg) in MeCN(10 ml) was stirred and heated at reflux for 17 hours. The solution was cooled and concentrated *in vacuo*. The residue was partitioned between EtOAc and water. The organic phase was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give Intermediate 9 as a white powder (203mg). LCMS showed $MH^+ = 346$; $T_{RET} = 2.84$min.

Intermediate 10: Ethyl 4-chloro-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



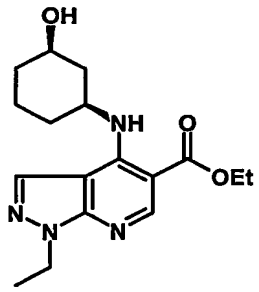
A mixture of 5-amino-1-ethylpyrazole (1.614g, 14.5mmol) and diethyl 2-(1-ethoxyethylidene)malonate (3.68g, 16.0mmol, as described by P.P.T. Sah, *J. Amer. Chem. Soc.*, 1931, 53, 1836) was heated at 150 °C under Dean Stark conditions for 5 hours. Phosphorous oxychloride (25ml) was carefully added to the mixture and the resulting solution was heated at 130 °C under reflux for 18 hours. The mixture was concentrated *in vacuo*, then the residual oil was carefully added, with cooling, to water (100ml). The resulting mixture was extracted with DCM (3x100ml) and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual oil was purified by Biotage chromatography (silica, 90g) eluting with EtOAc-petroleum ether (1:19). Fractions containing the desired product were combined and concentrated *in vacuo* to afford Intermediate 10 (1.15g). LCMS showed $MH^+ = 268$; $T_{RET} = 3.18$min.

Intermediate 11: Ethyl 1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



4-Aminotetrahydropyran hydrochloride (Intermediate 2A, 0.413g, 3.0mmol) was added to a mixture of Intermediate 10 (0.268g, 1.0mmol) and DIPEA (0.87ml, 5.0mmol) in MeCN (3ml). The resulting mixture was heated at 85 °C for 24 hours. Volatiles were removed *in vacuo* and the residue was dissolved in chloroform (1.5ml) and applied to a SPE cartridge (silica, 5g). The cartridge was eluted successively with Et_2O, EtOAc and EtOAc-MeOH (9/1). Fractions containing the desired product were combined and concentrated *in vacuo* to give the desired product contaminated with starting material (Intermediate 10). Further purification using a SPE cartridge (silica, 5g) eluting with EtOAc-cyclohexane (1:3) afforded Intermediate 11 (0.248g). LCMS showed $MH^+ = 333$; $T_{RET} = 2.75$min.

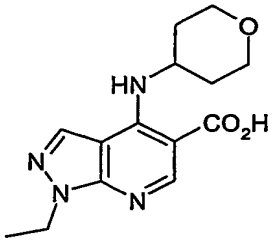
Intermediate 12: Ethyl 1-ethyl-4-{[(1*SR*,3*RS*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



[*cis*-(3-hydroxycyclohex-1-yl)amino group, racemic]

3-Aminocyclohexanol (0.677g, 5.9mmol, for example as described in *J. Chem. Soc., Perkin Trans 1,* 1994, 537 which describes the preparation of a 3.3 : 1 *cis* : *trans* mixture of 3-aminocyclohexanol) in MeCN(10ml) and EtOH (1ml) was added at room temperature to a stirred solution of Intermediate 1 (1.24g, 4.9mmol) and DIPEA (4.26ml, 24.5mmol) in MeCN (25ml). The resulting mixture was stirred at 85°C for 17h. The mixture was concentrated *in vacuo*, and the residue was partitioned between DCM (50ml) and water (10ml). The phases were separated and the organic phase was dried (Na_2SO_4) and evaporated to give an orange-brown oil. The oil was purified by Biotage chromatography (silica 100g) eluting with 30-50% EtOAc in cyclohexane to give Intermediate 12 as a white foam (0.68g). LCMS showed $MH^+ = 333$; $T_{RET} = 2.76$min.

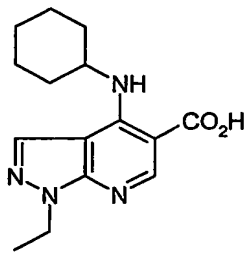
Intermediate 13: 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 4 (0.21g) in ethanol : water (95:5, 10ml) was treated with sodium hydroxide (0.12g). The mixture was heated at 50 °C for 8h, then concentrated *in vacuo*, dissolved in water and acidified to pH 4 with acetic acid. The resultant white solid was removed by filtration and dried *in vacuo* to afford Intermediate 13 as an off-white solid (0.156g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.11$min.

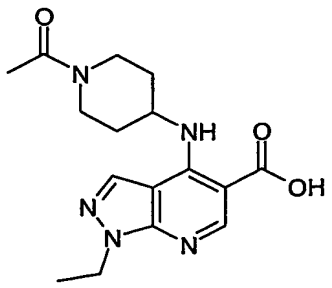
An alternative preparation of Intermediate 13 is as follows:
A solution of Intermediate 4 (37.8g) in ethanol : water (4:1, 375ml) was treated with sodium hydroxide (18.9g). The mixture was heated at 50 °C for 5 hours, then concentrated *in vacuo*, dissolved in water and acidified to pH 2 with aqueous hydrochloric acid (2M). The resultant white solid was removed by filtration and dried *in vacuo* to afford Intermediate 13 as an off-white solid (29.65g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.17$ min.

Intermediate 14: 4-(Cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



A solution of Intermediate 5 (5.37g, 17mmol) in EtOH (30ml) was treated with a solution of sodium hydroxide (2.72g, 68mmol) in water (20ml), and the resulting mixture was stirred at 50°C for 3h. The reaction mixture was concentrated *in vacuo*, dissolved in water (250ml) and the cooled solution was acidified to pH 1 with 5M-hydrochloric acid. The resultant solid was collected by filtration and dried *in vacuo* to afford Intermediate 14 as a white solid (4.7g). LCMS showed $MH^+ = 289$; $T_{RET} = 2.83$min.

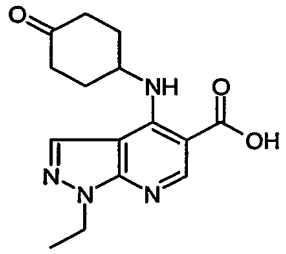
Intermediate 15: 4-[(1-Acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



Aqueous sodium hydroxide solution (8.55ml, 2M) was added to a solution of Intermediate 6 (1.55g) in EtOH (13ml). The mixture was heated at 50 °C for 18h then neutralised using aqueous hydrochloric acid and evaporated *in vacuo* to afford a mixture of 1-ethyl-4-(4-piperidinylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid and 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid.

Acetic acid (0.36ml) was added to a stirred mixture of HATU (2.41g) and DIPEA (2.21ml) in DMF (65ml). After stirring for 15 min the mixture was added to the mixture of 1-ethyl-4-(4-piperidinylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid and 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid and the reaction mixture was stirred for 15h. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography using Biotage (silica 90g), eluting with DCM : MeOH (0% - 5% MeOH) to afford Intermediate 15 (1.36g) as a white solid. LCMS showed MH^+ 334; T_{RET} = 2.06 min.

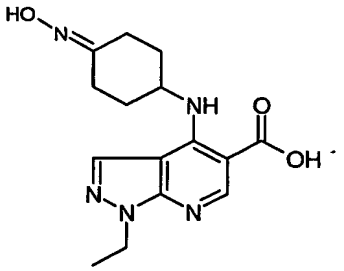
Intermediate 16: 1-Ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



A solution of sodium hydroxide (0.053g, 1.32mmol) in water (0.41ml) was added to a stirred solution of Intermediate 8 (0.1g, 0.303mmol) in ethanol (1ml), and the resulting mixture was heated at 50°C. After 1h, the cooled reaction mixture was adjusted to pH3 with 2M hydrochloric acid, and extracted with EtOAc (2 x 6ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give Intermediate 16 (0.072g) as a white solid. LCMS showed MH^+ = 303; T_{RET} = 2.13min.

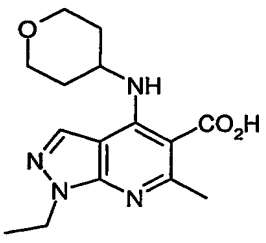
An alternative preparation of Intermediate 16 is as follows:
A solution of sodium hydroxide (0.792g, 19.8mmol) in water (6ml) was added to a stirred solution of Intermediate 8 (1.487g, 4.5mmol) in EtOH (15ml), and the resulting mixture was heated at 50°C. After 1 hour, the cooled reaction mixture was adjusted to pH4 with 2M hydrochloric acid, and extracted with EtOAc (3 x 30ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give Intermediate 16 (1.188g) as a white solid. LCMS showed $MH^+ = 303$; $T_{RET} = 2.12$min.

Intermediate 17: 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



A solution of Intermediate 16 (0.58g, 1.92mmol), hydroxylamine hydrochloride (0.26g, 3.74mmol) and DIPEA (0.65g, 5.03mmol) in MeCN (35ml) was stirred and heated at reflux for 3 hours, then cooled and left at room temperature overnight. Glacial AcOH (1 ml) was added, with stirring. The reaction mixture was concentrated *in vacuo*. EtOAc (10 ml) was added and the resultant suspension was stirred for 30 min. then applied to an SPE cartridge (silica, 20g). The cartridge was eluted with a (250:1) mixture of EtOAc and glacial AcOH, followed by a (500:16:1) mixture of EtOAc, MeOH and glacial AcOH, to give Intermediate 17 (0.327g) as a white solid. LCMS showed $MH^+ = 318$; $T_{RET} = 2.21$min.

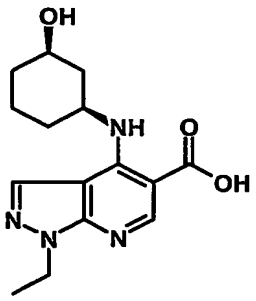
Intermediate 18: 1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



2M-Sodium hydroxide solution (0.75ml, 1.5mmol) was added to Intermediate 11 (0.248g, 0.75mmol) in EtOH (2ml), and the mixture was heated at reflux for 16 hours. The reaction mixture was concentrated, diluted with water (1ml) and acidified with 2M-

hydrochloric acid (0.75ml) to precipitate a solid which was collected by filtration to afford Intermediate 18 (0.168g). LCMS showed $MH^+ = 305$; $T_{RET} = 1.86$min.

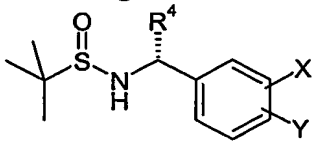
Intermediate 19: 1-Ethyl-4-{[(1*SR*,3*RS*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



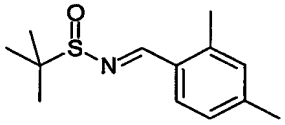
(*cis*-3-hydroxycyclohex-1-ylamino group, racemic)

A solution of Intermediate 12 (0.681g, 2.05mmol) in EtOH (7ml) was treated with a solution of sodium hydroxide (0.362g, 9.05mmol) in water (2.9ml). The resulting mixture was stirred at 50°C. After 3h, the reaction mixture was concentrated *in vacuo* to give a residual oil which was dissolved in water (3ml), then cooled and acidified to pH 3 with 2M hydrochloric acid. After stirring at 0°C for 1h, the resulting precipitate was collected by filtration, washed with cooled water (0.5ml) and dried *in vacuo* to afford Intermediate 19 as a white solid (0.491g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.14$min.

Intermediates 20-86

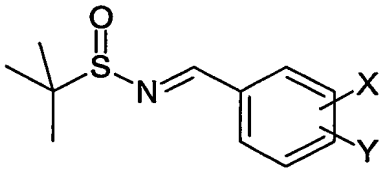
These intermediates were prepared using a modification of the procedure developed by D. A. Cogan, G. Liu and J. Ellman and described in *Tetrahedron*, 1999, *55*, 8883-8904. In the Cogan,, Liu, Ellman paper, the use of (S)-tert butyl sulphinamide in chemistry similar to that described in Intermediates 20-86 below allegedly produced an enrichment in a diastereoisomer with the general stereochemistry at the carbon atom next to the nitrogen shown here:  (i.e. inserted group R4 into the paper as shown, branched-benzyl is illustrative example only); this stereochemistry (R4 into the paper) was formed in the carbon-carbon bond forming reaction (i.e. before any optional separation of diastereoisomers). Therefore, compounds containing an alpha substituent on the benzylic carbon atom (Intermediates 37-86) are believed to be enriched in an enantiomer/diastereoisomer which is believed to have the (R)-stereochemistry at the benzylic carbon atom.

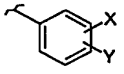
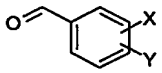
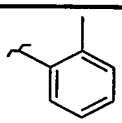
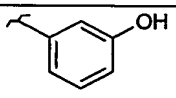
Intermediate 20: **N-[(1*E*)-(2,4-dimethylphenyl)methylidene]-2-methyl-2-propanesulfinamide**

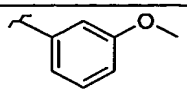
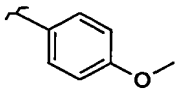
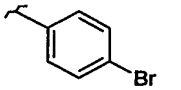
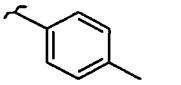
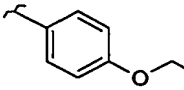
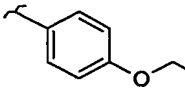
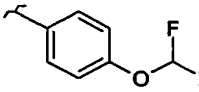
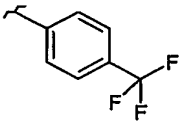
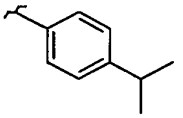
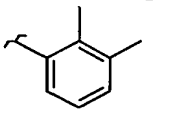
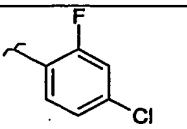
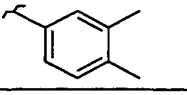
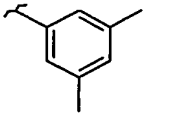
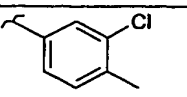


A solution of (S)-tert butyl sulphinamide (0.20g, 1.65mmol) in THF (2ml) was added to 2,4-dimethylbenzaldehyde (0.22g, 1.57mmol) (e.g. available from Aldrich). The solution was made up to 10ml with THF. Titanium (IV) ethoxide (0.75g, 3.38mmol) was added and the reaction mixture was heated at 75° for 2 hours. The reaction mixture was cooled and poured onto saturated brine, with vigorous stirring. Celite was added to the resulting suspension, which was filtered and washed with DCM. The organic phase was separated from the aqueous phase by passing through a hydrophobic frit. The DCM was evaporated. The residue was purified on a 50g SPE cartridge, eluting first with a (9:1) mixture of cyclohexane and EtOAc and then with a (4:1) mixture of cyclohexane and EtOAc. Fractions containing the required product were combined and concentrated *in vacuo* to give Intermediate 20 (0.29g) as a white solid. LCMS showed $MH^+ = 238$; $T_{RET} = 3.43$min.

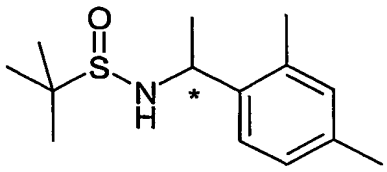
The following intermediates 21-36 were prepared in a similar manner from (S)-tert butyl sulphinamide and the appropriate commercially available aldehyde (substituted benzaldehyde):



Intermediate no.		**MH^+ ion**	**T_{RET} (min)**	**Optional: One Possible Commercial Supplier of Aldehyde Starting Material (if known)** 	**Literature Reference to Intermediate (if known)**
21		224	3.25	Aldrich	
22		226	2.85	Aldrich	

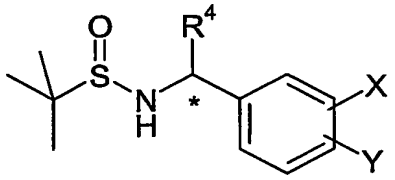
23.		240	3.06	Aldrich	
24		240	3.03	Aldrich	Tetrahedron, 1999, **55**, 8883-8904
25		287 & 289	3.36	Aldrich	Tetrahedron Asymm.; 2002, **13**, 303-310
26		224	3.2	Aldrich	
27		254	3.32	Aldrich	
28		269	3.31	Aldrich	
29		276	3.27	Fluorochem Ltd.	
30		278	3.46	Aldrich	J. Org. Chem; 2003, **68**, 6894-6898
31		252	3.53	Aldrich	
32		238	3.40	Aldrich	
33		262	3.42	Acros Organics	
34		239	3.41	Lancaster	
35		238	3.38	Lancaster	
36		258	3.56	Aldrich	

Intermediate 37: N-[1-(2,4-dimethylphenyl)ethyl]-2-methyl-2-propanesulfinamide

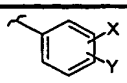
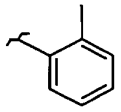
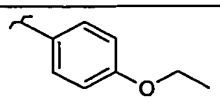


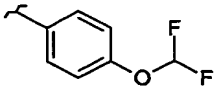
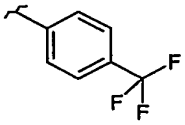
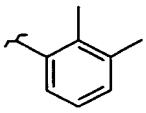
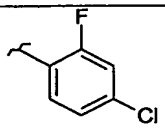
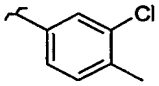
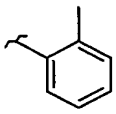
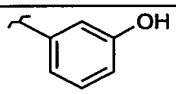
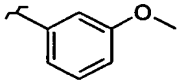
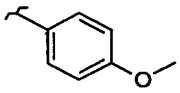
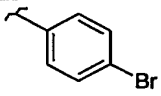
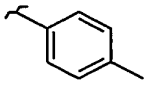
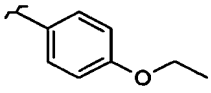
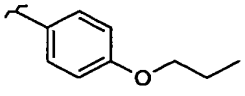
A 3.0 Molar solution of methyl magnesium bromide in Et_2O (2.6ml) was added dropwise, with stirring, to a solution of Intermediate 20 (0.14g, 0.59mmol) in dry THF (5ml) at –10°C. The reaction mixture was stirred at –10°C for 3 hours then gradually warmed to 20°C over 24 hours. The reaction mixture was cooled to 0 °C and treated, dropwise, with saturated ammonium chloride, with vigorous stirring. Once effervescence had ceased more ammonium chloride (5ml) was added, followed by DCM (30ml). The reaction mixture was stirred for 30 min. then the organic phase was filtered through a hydrophobic frit. The DCM was evaporated to leave Intermediate 37 (0.15g) as a white solid (mixture of diastereoisomers, believed to be enriched in a diastereoisomer which is believed to have the (R)-stereochemistry at the benzylic carbon atom). LCMS showed $MH^+ = 254$; $T_{RET} = 3.13$min.

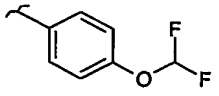
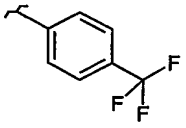
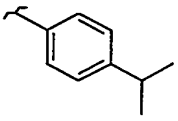
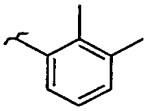
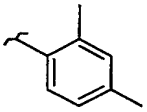
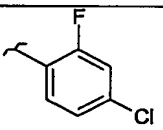
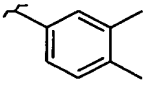
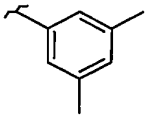
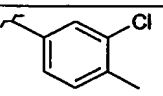
The following Intermediates 38-61 were prepared in a similar manner from Intermediates 20-36, using either a 3.0 Molar solution of methylmagnesium bromide in diethyl ether (R^4 = Me) or a 3.0 Molar solution of ethylmagnesium bromide in diethyl ether (R^4 = Et):



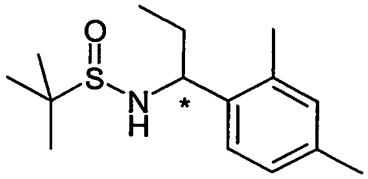
(believed to be enriched in a diastereoisomer which is believed to have the (R)-stereochemistry at the benzylic carbon atom)

Intermediate no.	R^4		Precursor	MH^+ ion	T_{RET} (min)	Reference (if known)
38	Me		Intermediate 21	240	2.95	
39	Me		Intermediate 27	270	2.97	

40	Me		Intermediate 29	292	3.00	
41	Me		Intermediate 30	294	3.17	
42	Me		Intermediate 32	254	3.10	
43	Me		Intermediate 33	278	3.16	
44	Me		Intermediate 34	274	3.25	
45	Et		Intermediate 21	254	3.10	
46	Et		Intermediate 22	256	2.56 & 2.69	
47	Et		Intermediate 23	270	2.86 & 2.94	
48	Et		Intermediate 24	270	2.86 & 2.93	Tetra-hedron, 1999, **55**, 8883-8904
49	Et		Intermediate 25	317 & 319	3.17	
50	Et		Intermediate 26	254	3.14	
51	Et		Intermediate 27	284	3.16	
52	Et		Intermediate 28	298	3.24 & 3.28	

53	Et		Intermediate 29	306	3.18	
54	Et		Intermediate 30	308	3.30	
55	Et		Intermediate 31	282	3.43	
56	Et		Intermediate 32	268	3.24	
57	Et		Intermediate 20	268	3.28	
58	Et		Intermediate 33	292	3.30	
59	Et		Intermediate 34	268	3.26 & 3.31	
60	Et		Intermediate 35	268	3.28 & 3.33	
61	Et		Intermediate 36	288	3.3	

Separation of the diastereoisomers of Intermediate 57



The mixture of diastereoisomers (Intermediate 57: 3g) were purified by short path chromatography on silica, using cyclohexane containing 10-50% ethyl acetate as the eluent, to give the two diastereoisomers of Intermediate 57, as follows:

Intermediate 57a (Diastereoisomer 1):

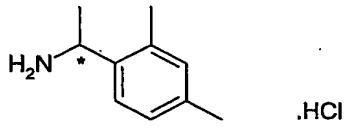
Isolated yield = 322mg (minor diastereomer, believed to have the (S)-stereochemistry at the benzylic carbon atom).

LCMS showed $MH^+ = 268$; $T_{RET} = 3.23$min.

Intermediate 57b (Diastereoisomer 2):
Isolated yield = 1.76g (major diastereomer, believed to have the (R)-stereochemistry at the benzylic carbon atom).
LCMS showed $MH^+ = 268$; $T_{RET} = 3.23$min.

See Tim Tec Building Blocks B for the racemate of the following Intermediate 62:

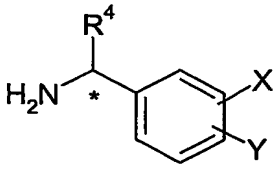
Intermediate 62: **1-(2,4-dimethylphenyl)ethyl]amine hydrochloride**



(Believed to be a mixture of enantiomers with the major enantiomer believed to have the (R)-stereochemistry)

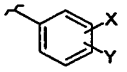
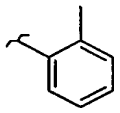
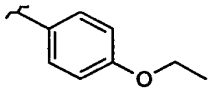
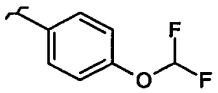
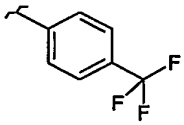
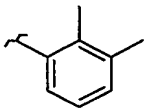
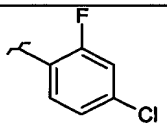
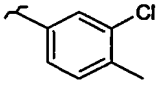
A solution of Intermediate 37 (151mg, 0.60mmol) in a mixture of 4.0M hydrogen chloride in dioxan (1ml) and MeOH (1ml) was left to stand for 1 hour. The solvents were evaporated. The residue was triturated in Et_2O containing a few drops of MeOH to give a solid suspension. The solid was filtered off and dried to give Intermediate 62 (76mg) as a white solid. LCMS showed $MH^+ = 150$; $T_{RET} = 1.84$min.

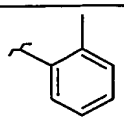
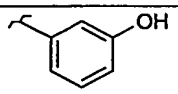
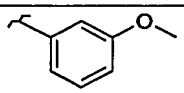
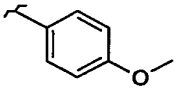
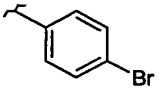
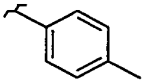
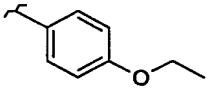
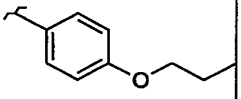
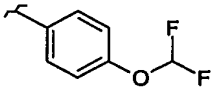
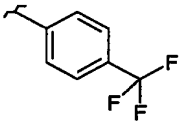
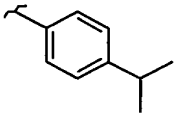
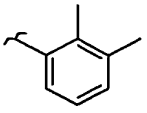
The following Intermediates 63-86 were prepared in a similar manner from Intermediates 38-61:

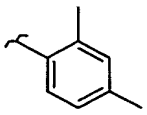
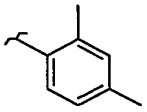
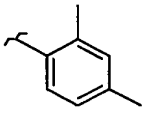
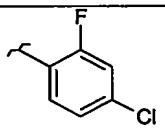
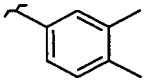
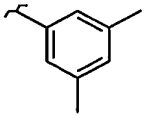
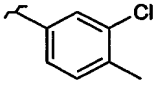


.HCl

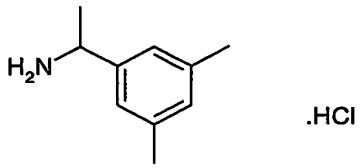
(Except for Intermediates 82a and 82b, Intermediates 63-86 are believed to be a mixture of enantiomers with the major enantiomer believed to have the (R)-stereochemistry)

Inter-mediate no.	**R4**		**Precursor**	**MH^+ ion**	**T_{RET} (min)**	**Publication Reference to or One Possible Commercial Supplier of Intermediate (if known):** reference may be made to the racemate and/or the (R)-enantiomer
63	Me		Intermediate 38	136	1.33	ACB Blocks Product List
64	Me		Intermediate 39	[MH-16] = 149	1.77	ACB Blocks Product List
65	Me		Intermediate 40	188	1.65	Braz. Pedido Pl; 1989, BR8804596
66	Me		Intermediate 41	190	1.88	ACB Blocks Product List
67	Me		Intermediate 42	150	1.81	Agr. And Biol. Chem; 1973, **37**, 981-988
68	Me		Intermediate 43	174	1.60	
69	Me		Intermediate	169	1.95	European Patent Application

			44			EP191496 A2 (1986)
70	Et		Intermediate 45	150	1.81	Tetrahedron Lett.; 1986, **27**, 1331-1334
71	Et		Intermediate 46	152	1.16	
72	Et		Intermediate 47	166	1.69	PCT Patent Appl. WO2002083624 (2002)
73	Et		Intermediate 48	166	1.67	Tetrahedron Lett.; 1998, **39**, 3559-3562
74	Et		Intermediate 49	214 & 216	1.9	Synthesis, 1999, 930-934
75	Et		Intermediate 50	150	1.78	Tetrahedron Asymm.; 1999, **10**, 1579-1588
76	Et		Intermediate 51	[M-16] = 163	1.96	
77	Et		Intermediate 52	194	2.07	
78	Et		Intermediate 53	202	1.95	Pesticide Sci; 1998, **54**, 223
79	Et		Intermediate 54	204	2.12	PCT Patent Appl. WO2002051809 (2002)
80	Et		Intermediate 55	178	2.1	
81	Et		Intermediate 56	164	2.01	

82	Et		Intermediate 57	164	2.04	
82a	Et		Intermediate 57a (Diastereo-isomer 1)			Intermediate 82a enantiomer is believed to have the (S)-stereochemistry at the benzylic carbon atom
82b	Et		Intermediate 57b (Diastereo-isomer 2)			Intermediate 82b enantiomer is believed to have the (R)-stereochemistry at the benzylic carbon atom
83	Et		Intermediate 58	188	1.93	
84	Et		Intermediate 59	164	2.00	PCT Patent Appl. WO2002083624 (2002)
85	Et		Intermediate 60	164	2.04	PCT Patent Appl. WO2002083624 (2002)
86	Et		Intermediate 61	185	2.13	

Intermediate 87: [1-(3,5-dimethylphenyl)ethyl]amine hydrochloride (Jpn. Kokai Tokkyo Koho JP 62294669 (1987))

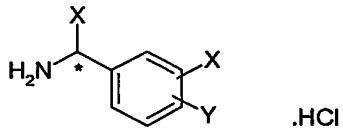


(Racemic)

A mixture of (3,5-dimethyl)acetophenone (0.95g, 7.0mmol) (e.g. available from Lancaster Synthesis), formamide (1.4ml, 1.58g, 35.0mmol) and formic acid (0.81ml,

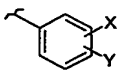
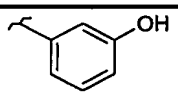
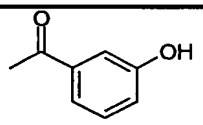
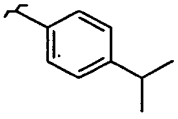
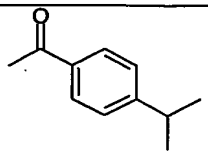
0.97g, 21.0 mmol) was heated at 160^0 for 18 hours. The reaction mixture was cooled and partitioned between EtOAc and water. The organic phase was separated, washed with potassium carbonate solution and sodium chloride solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was treated with 2M hydrochloric acid (10ml) and the resultant mixture was heated at reflux for 18 hours, cooled to room temperature and washed with DCM (2x10ml). The aqueous solution was concentrated *in vacuo* to leave Intermediate 87 (0.42g) as a white solid. LCMS showed $MH^+ = 150$; $T_{RET} = 1.88$min.

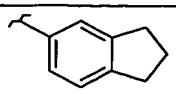
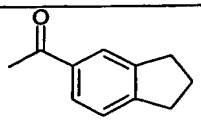
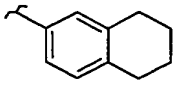
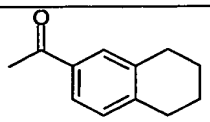
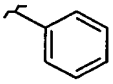
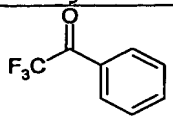
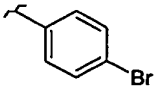
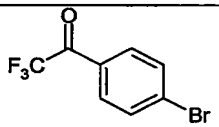
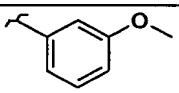
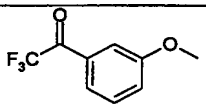
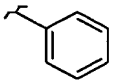
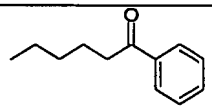
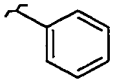
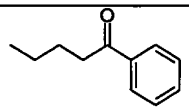
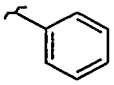
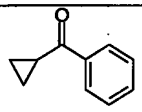
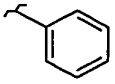
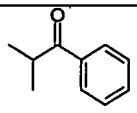
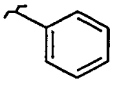
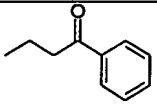
The following racemic Intermediates 88-99 were made in a similar manner from the appropriate acetophenone derivative, i.e. compound X-C(O)-Ar where Ar is optionally substituted phenyl or phenyl fused to C5-6cycloalkyl and X is R^4 or R^5 (commercially available unless stated):



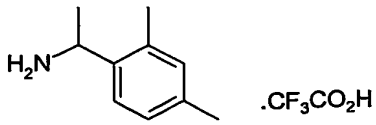
.HCl

(Racemic)

Inter-mediate no.	**X**		**Precursor (and one Possible Commercial Supplier - Optional)**	**MH^+ ion**	**T_{RET} (min)**	**Publication Reference to or One Possible Commercial Supplier of Intermediate (if known):** reference may be made to the racemate and/or the (R)-enantiomer
88	Me		 Aldrich	138	2.29	Tetrahedron, 1977, **33**, 489
89	Me		 Lancaster Synthesis	164	2.04	Tim Tec Building Blocks B

90	Me		 Avocado	162	1.91	Jpn. Kokai Tokkyo Koho JP 07101939 A2 (1995)
91	Me		 Lancaster Synthesis	176	2.13	Jpn. Kokai Tokkyo Koho JP 07101939 A2 (1995)
92	CF_3		 Aldrich	176	1.55	Microchemistry Building Blocks
93	CF_3		 Aldrich	255	2.53	Angew. Chem. Int. Ed; 2001, **40**, 589-590
94	CF_3		 SALOR	206	1.94	
95	-$(CH_2)_4CH_3$		 Aldrich	178	2.24	J. Combinatorial Chem; 2001, **3**, 71-77
96	-$(CH_2)_3CH_3$		 Aldrich	164	2.00	Civentichem.
97			 Aldrich	148	0.90	ACB Blocks
98	-$CH(CH_3)_2$		 Aldrich	150	1.71	Civentichem.
99	-$(CH_2)_2CH_3$		 Aldrich	150	1.79	Heterocyclic Compounds Catalog

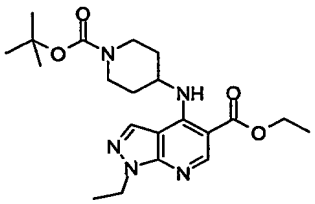
Intermediates 100-101: [1-(2,4-dimethylphenyl)ethyl]amine trifluoroacetate



[(R)- and (S)- enantiomers]

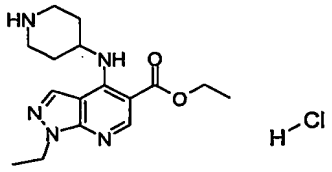
Intermediate 62 (0.40g) was resolved by preparative chiral column chromatography, using a 2-inch x 20cm ChiralCel OJ column with a (2:98) mixture of heptane and ethanol, containing 0.1% trifluoroacetic acid, as the eluent. Intermediate 100 (first enantiomer to elute: 0.21g) and Intermediate 101 (second enantiomer to elute: 0.12g) were separated on the column. LCMS showed $MH^+ = 150$; $T_{RET} = 1.76$min. for both enantiomers.

Intermediate 102: Ethyl 4-[(1-{[(1,1-dimethylethyl)oxy]carbonyl}-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



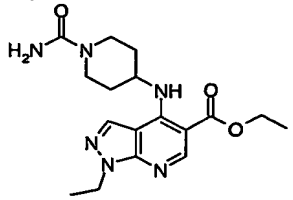
A solution of Intermediate 1 (2.3g) in acetonitrile (50ml) was treated with solid 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate (2g, e.g. available from AstaTech) and DIPEA (8.6ml). The reaction mixture was heated at 90°C for 16h. The solvents were removed under reduced pressure and the residue was partitioned between DCM (100ml) and water (75ml). The organic fraction was collected through a hydrophobic frit and the solvents were removed under reduced pressure to yield Intermediate 102 as a white solid (3.9g). LCMS showed $MH^+ = 418$; $T_{RET} = 3.35$min.

Intermediate 103: Ethyl 1-ethyl-4-(4-piperidinylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate hydrochloride



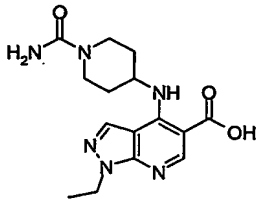
Intermediate 102 (3.9g) was treated with 4.0M hydrogen chloride in 1,4-dioxane (30ml) and the reaction mixture was stirred at 22°C for 1h. The solvents were removed to give Intermediate 103 as a white solid (3.9g). LCMS showed $MH^+ = 318$; $T_{RET} = 2.21$min.

Intermediate 104: Ethyl 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



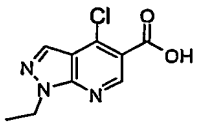
A suspension of Intermediate 103 (3.9g) in THF (100ml) was treated with trimethylsilyl isocyanate (1.99ml) followed by DIPEA (2.6ml) and the solution was stirred at 22°C for 2h. The volatile solvents were removed under reduced pressure and the residue was partitioned between DCM (50ml) and water (25ml). The organic layer was collected. The aqueous phase was re-extracted with DCM (50ml). The organic layers were combined, separated from water by passing through a hydrophobic frit and concentrated under reduced pressure to yield Intermediate 104 as a white solid (3.9g). LCMS showed MH^+ = 361; T_{RET} = 2.45min.

Intermediate 105: 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 104 (3.9g) in ethanol (50ml) was treated with a solution of sodium hydroxide (1.77g) in water (20ml) and the reaction mixture was heated at 80°C for 16h. LCMS indicated that partial hydrolysis of the urea portion had occurred. The solvents were removed and the residue was dissolved in water (5ml), the pH was adjusted to 3 (2M HCl) and the resultant white precipitate was collected by filtration and dried. This precipitate was dissolved in ethanol. The solution was treated with trimethylsilyl isocyanate (3ml) and DIPEA (10ml) and then stirred at 22°C for 16h. The solvents were removed and the residue was dissolved in water (5ml), the pH was adjusted to 3 (2M HCl) and the resultant white precipitate was collected by filtration and dried to give Intermediate 105 as a white solid (2.66g). LCMS showed MH^+ = 333; T_{RET} = 2.00min.

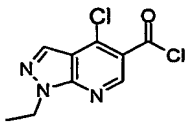
Intermediate 106: 4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



A solution of Intermediate 1 (20g) in 1,4-dioxane (100ml) was treated with a solution of potassium hydroxide (18g) in water (30ml) and the reaction mixture was stirred at 22°C for 24h. The solvent was evaporated and the residue was acidified to pH 3 (2M HCl). The resultant white precipitate was collected by filtration and dried to give Intermediate 106 as a white solid (16.9g). LCMS showed $MH^+ = 226$; $T_{RET} = 2.45$min.

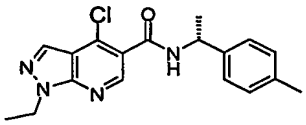
Alternative synthesis: A solution of Intermediate 1 (3.5g) in dioxane (28ml) was treated with potassium hydroxide (6.3g) as a solution in water (20ml). The mixture was stirred for 2h, then concentrated in vacuo, acidified to pH 3 with 2M aqueous hydrochloric acid and extracted with ethyl acetate. The layers were separated, the organic layer dried over sodium sulphate, then concentrated in vacuo to afford Intermediate 106 as a white solid (2.4g). LCMS showed $MH^+ = 226$; $T_{RET} = 2.62$min.

Intermediate 107: 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl chloride



A solution of Intermediate 106 (17.8g) in thionyl chloride (100ml) was heated under reflux for 3.5h. The solution was cooled to room temperature. The thionyl chloride was removed *in vacuo* and any remaining thionyl chloride was removed by azeotropic distillation with toluene (30ml) to give Intermediate 107 as a beige solid (16.8g). LCMS (MeOH solution) showed $MH^+ = 240$ (Methyl ester); $T_{RET} = 2.88$min.

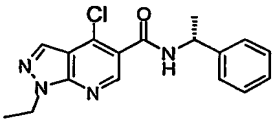
Intermediate 108: 4-chloro-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



A solution of Intermediate 107 (2.0g) in THF (20ml) was treated with (R)-(+)-1-(4-methylphenyl) ethylamine (1.11g) (e.g. available from Lancaster Synthesis) and DIPEA (1.06g). The reaction mixture was stirred at 22°C for 24h. The solvent was evaporated and the residue was dissolved in DCM (50ml). The solution was washed with 5% citric acid solution (50ml) and 0.5M sodium bicarbonate solution (50ml), dried (Na_2SO_4), filtered and concentrated to give Intermediate 108 as a white solid (1.61g). LCMS showed $MH^+ = 343$; $T_{RET} = 3.22$min.

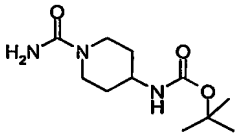
The following Intermediate 109 was prepared in an analogous manner, suitably from (R)-(+)-1-phenylethylamine (e.g. available from Aldrich):

Intermediate 109: 4-chloro-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



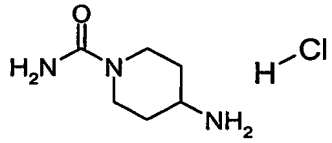
LCMS showed $MH^+ = 329$; $T_{RET} = 3.0$min.

Intermediate 110: 1,1-dimethylethyl [1-(aminocarbonyl)-4-piperidinyl]carbamate



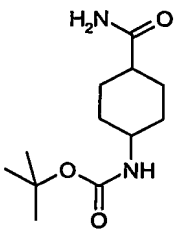
A solution of 1,1-dimethylethyl 4-piperidinylcarbamate (0.35g, e.g. available from Syngene or AstaTech) in DCM (10ml) was treated with trimethylsilyl isocyanate (1.1ml). The reaction mixture was stirred at 22°C for 72h. The mixture was diluted with saturated $NaHCO_3$ solution (20ml). The organic phase was collected through a hydrophobic frit and evaporated to give Intermediate 110 as a white foam (0.29g). ^{1}H NMR (400MHz in $CDCl_3$, 27°C, δ ppm) 4.45 (br. s, 3H). 3.90 (d, 2H), 3.65 (br. m, 1H), 2.9-3.0 (dt, 2H), 1.95-2.0 (br. dd, 2H), 1.45 (s, 9H), 1.3-1.4 (dq, 2H).

Intermediate 111: 4-amino-1-piperidinecarboxamide hydrochloride



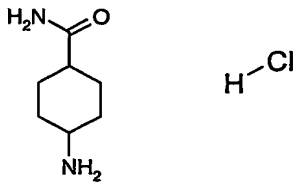
A solution of intermediate 110 (0.29g) in 4.0M hydrogen chloride in 1,4-dioxane (5ml) was stirred at 22°C for 4h. The solvent was evaporated to give Intermediate 111 as a white foam (0.27g). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δ ppm) 8.1 (br. s, 2H), 3.95 (d, 2H), 3.15 (m, 1H), 2.7 (dt, 2H), 1.85 (dd, 2H), 1.35 (m, 2H).

Intermediate 112: 1,1-dimethylethyl [4-(aminocarbonyl)cyclohexyl]carbamate



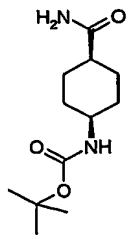
A solution of 4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexanecarboxylic acid (from Fluka, 1g) in DMF (30ml) was treated with HATU (1.72g) and DIPEA (5.4ml). The reaction mixture was stirred at 22°C for 10 min. A 0.5M solution of ammonia in 1,4-dioxane (40ml) was added and the reaction mixture was stirred at 22°C for 72h. The solvents were evaporated and the residue was purified by loading the crude mixture onto a 50g aminopropyl SPE cartridge and eluting with ethyl acetate (100ml), then methanol (100ml). Intermediate 112 was isolated by evaporation of the methanol fraction as a yellow oil (0.99g). LCMS showed $MH^+ = 242$; $T_{RET} = 2.2$min.

Intermediate 113: 4-aminocyclohexanecarboxamide hydrochloride



4.0M hydrogen chloride in 1,4-dioxane (14ml) was added to Intermediate 112 (0.99g) and the reaction mixture was stirred at 22°C for 30min. The solvent was evaporated to give Intermediate 113 as a yellow gum (1.03g). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) 7.9 (br. S, 2H), 3.9 (br. S, 2H), 3.10 (m, 1H), 1.92 (m, 2H), 1.68 (m, 4H), 1.50 (m, 2H).

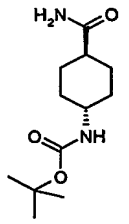
Intermediate 114: 1,1-dimethylethyl [*cis*-4-(aminocarbonyl)cyclohexyl]-carbamate



A solution of *cis*-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexane-carboxylic acid (5.0g) (e.g. available from Fluka), EDC (5.9g) and HOBT (4.17g) was stirred for 20 min. Ammonia solution (Specific Gravity = 0.88; 8ml) was added. The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo* and partitioned between DCM and saturated sodium bicarbonate solution. The aqueous phase was separated and washed with DCM. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to give Intermediate 114 (4.84g) as a white solid. LCMS showed $MH^+ = 243$; $T_{RET} = 2.3$min.

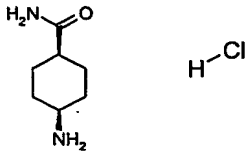
The following Intermediate 115 was prepared in a similar manner from *trans*-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexanecarboxylic acid (e.g. available from Fluka):

Intermediate 115: 1,1-dimethylethyl [*trans*-4-(aminocarbonyl)cyclohexyl]-carbamate



LCMS showed $MNH_4^+ = 260$; $T_{RET} = 2.24$min.

Intermediate 116: *cis*-4-aminocyclohexanecarboxamide hydrochloride

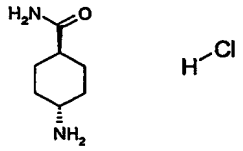


4.0M HCl in dioxan (50ml) was added to a stirred solution of Intermediate 114 (4.84g) in dioxan (100ml). The reaction mixture was stirred for 1 hour at room temperature and then

left at 0°C for 3 days. The reaction mixture was concentrated *in vacuo* to give Intermediate 116 (4.1g) as a white solid. LCMS showed $MH^+ = 143$; $T_{RET} = 0.31$min.

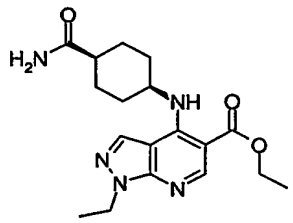
The following Intermediate 117 was prepared in a similar manner from Intermediate 115:

Intermediate 117: *trans*-4-aminocyclohexanecarboxamide hydrochloride



LCMS showed $MH^+ = 143$; $T_{RET} = 0.30$min.

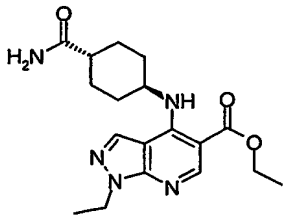
Intermediate 118: ethyl 4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



A solution of Intermediate 1 (2.0g), Intermediate 116 (1.55g) and DIPEA (6.9ml) in ethanol (140ml) was stirred and heated at reflux overnight. More of Intermediate 116 (420mg) and DIPEA (3.5ml) were added. The reaction mixture was stirred and heated at reflux overnight, cooled and concentrated *in vacuo*. The residue was partitioned between DCM and saturated sodium bicarbonate solution. The organic phase was concentrated *in vacuo*. The residue was triturated in a mixture of DCM and cyclohexane to give a solid. The solid was filtered off and dried to give Intermediate 118 (2.16g) as a yellow solid. LCMS showed $MH^+ = 360$; $T_{RET} = 2.56$min.

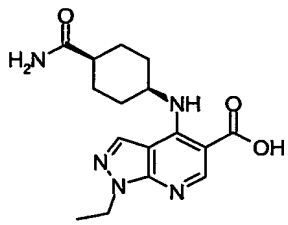
The following Intermediate 119 was prepared in a similar manner from Intermediate 1 and Intermediate 117:

Intermediate 119: ethyl 4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



LCMS showed $MH^+ = 360$; $T_{RET} = 2.84$min.

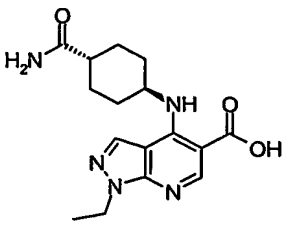
Intermediate 120: **4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid**



A mixture of Intermediate 118 (1.54g) and sodium hydroxide (0.68g) in 95% aqueous EtOH (EtOH containing 5% water) (60ml) was stirred and heated at 50°C overnight. The solvent was removed *in vacuo*. The residue was dissolved in water. The solution was cooled to 0-5°C, with stirring, and acidified with 2M HCl. The resultant suspension was refrigerated for 3 days then filtered under suction. The residue was dried in a vacuum oven to give Intermediate 120 (1.58g) as a yellow solid. LCMS showed $MH^+ = 332$; $T_{RET} = 2.06$min.

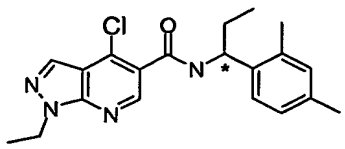
The following Intermediate 121 was prepared in an analogous manner from Intermediate 1 and Intermediate 119:

Intermediate 121: **4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid**



LCMS showed $MH^+ = 332$; $T_{RET} = 2.06$min.

Intermediate 122: **4-chloro-*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide**



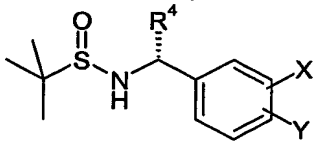
(Believed to be a mixture of enantiomers with the major enantiomer believed to have the (R)-stereochemistry)

Prepared from Intermediates 82 and 107 using a method analogous to that used to make Intermediate 108.

LCMS showed $MH^+ = 371$; $T_{RET} = 3.32$min.

Intermediates 123 to 145, 50a, 55a, 58a, 75a, 80a and 83a

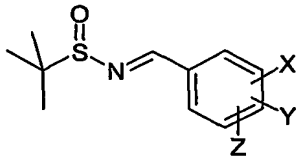
Like Intermediates 20-86, these intermediates were prepared using a modification of the procedure developed by D. A. Cogan, G. Liu and J. Ellman and described in *Tetrahedron*, 1999, *55*, 8883-8904. In the Cogan,, Liu, Ellman paper, the use of (S)-tert butyl sulphinamide in chemistry similar to that described in Intermediates 123-127 and 128-136 below allegedly produced an enrichment in a diastereoisomer with the general stereochemistry at the carbon atom next to the nitrogen shown here:

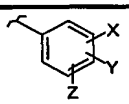
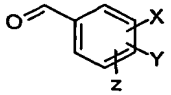
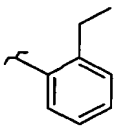
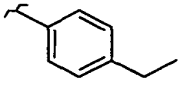
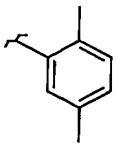
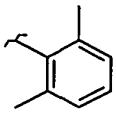
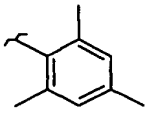


(i.e. inserted group R4 into the paper as shown, branched-benzyl is illustrative example only); this stereochemistry (R4 into the paper) was formed in the carbon-carbon bond forming reaction (i.e. before any optional separation of diastereoisomers). As the process of Intermediates 128-136, 50a, 55a and 58a herein includes an additional step separating the diastereomers, the compounds containing an alpha substituent on the benzylic carbon atom (Intermediates 128 to 136, 50a, 55a and 58a, and Intermediates 137 to 145, 75a, 80a and 83a) are believed to consist essentially of an enantiomer / diastereoisomer which is believed to have the (R)-stereochemistry at the benzylic carbon atom.

Intermediates 123 to 127

The following Intermediates 123 to 127 were prepared from (S)-tert butyl sulphinamide and the appropriate commercially available aldehyde (substituted benzaldehyde), by adopting a similar method to that used to prepare Intermediate 20:



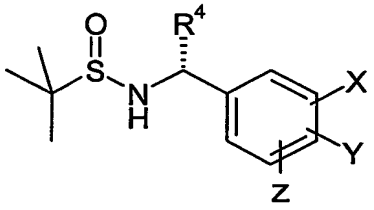
Intermediate no.		**MH^+ ion**	**T_{RET} (min)**	**One Possible Commercial Supplier of Aldehyde Starting Material (if known)** 
123				Aldrich
124		238	3.43	Aldrich
125		238	3.31	Aldrich
126		238	3.27	Aldrich
127		252	3.55	Avocado Research

Intermediates 128 to 136, 50a, 55a and 58a

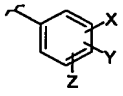
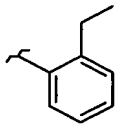
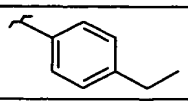
Intermediate 128 synthesis

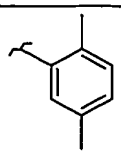
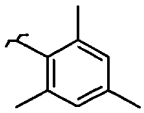
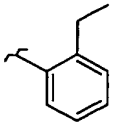
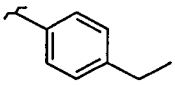
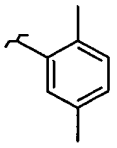
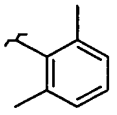
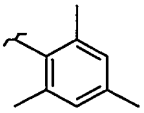
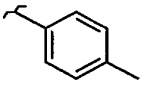
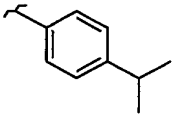
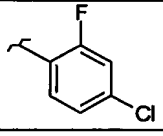
A 3.0 Molar solution of methylmagnesium bromide in diethyl ether (3.8 ml) was added to a stirred solution of Intermediate 123 (0.91 g) in dry DCM (20ml) at –78 °C. The reaction mixture was stirred at –78 °C for 1 hour, warmed to room temperature and stirred at room temperature for 24 h. The reaction mixture was cooled again to –78 °C. More 3.0 Molar methylmagnesium bromide solution in diethyl ether (1.9 ml) was added. The reaction mixture was stirred at –78 °C for 1 hour, warmed to room temperature and stirred at room temperature for 2 h, then cooled to 0 °C and treated dropwise with stirring with saturated ammonium chloride solution (10 ml) followed by DCM (20 ml). The organic phase was filtered through a hydrophobic frit. The DCM was evaporated. The residue was purified on a 50 g silica SPE cartridge, using cyclohexane containing a gradient of 0% to 100% ethyl acetate. The fractions containing the major diastereoisomer (e.g. can be eluted using 100% ethyl acetate) were combined and evaporated to give Intermediate 128 as a solid. LCMS showed $MH^+ = 254$, $T_{RET} = 3.07$ or 3.12.

The following **Intermediates 129 to 136, 50a, 55a and 58a** were prepared from Intermediates 124 to 127, 26, 31 or 33 in the same or a similar manner to that described above for Intermediate 128, using either a 3.0 Molar solution of methylmagnesium bromide in diethyl ether (R^4 = Me) or a 3.0 Molar solution of ethylmagnesium bromide in diethyl ether (R^4 = Et):



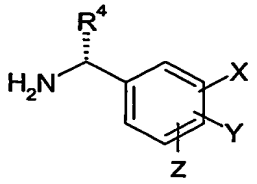
(Intermediates 128 to 136, 50a, 55a and 58a are believed to consist essentially of an isomer believed to have the (R)-stereochemistry at the benzylic carbon atom.)

Inter-mediate no.	R^4		Precursor	MH^+ ion	T_{RET} (min)
128	Me		Intermediate 123	254	3.12
129	Me		Intermediate 124	254	3.15

130	Me		Intermediate 125	254	3.11
131	Me		Intermediate 127	268	3.21
132	Et		Intermediate 123		
133	Et		Intermediate 124	268	3.27
134	Et		Intermediate 125	268	3.17
135	Et		Intermediate 126		
136	Et		Intermediate 127	282	3.33
50a	Et		Intermediate 26		
55a	Et		Intermediate 31		
58a	Et		Intermediate 33		

Intermediates 137 to 145, 75a, 80a and 83a

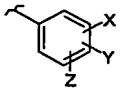
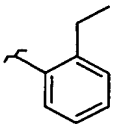
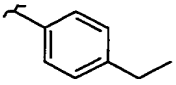
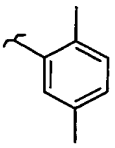
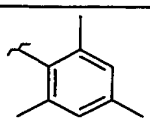
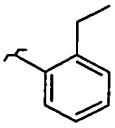
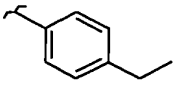
The following Intermediates 137 to 145, 75a, 80a and 83a were prepared, in a similar manner to that described for the synthesis of Intermediate 62, from Intermediates 128 to 136, 50a, 55a or 58a:

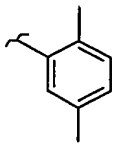
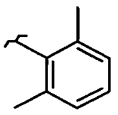
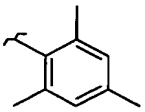
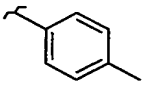
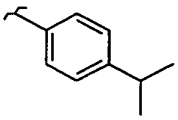
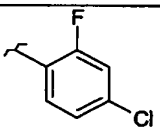


.HCl

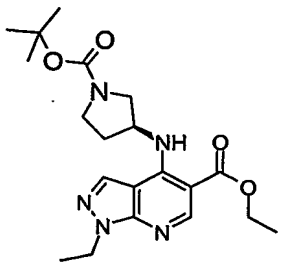
(Intermediates 137 to 145, 75a, 80a and 83a are believed to consist essentially of an enantiomer believed to have the (R)-stereochemistry at the benzylic carbon atom.)

5

Inter-mediate no.	**R^4**		**Precursor**	**MH^+ ion**	**T_{RET} (min)**	**Publication Reference to, or a Possible Commercial Supplier of, Intermediate (if known):** reference may be made to the racemate and/or the (R)-enantiomer
137	Me		Intermediate 128			CAS 104338-67-2 (Chem. Abs. Service)
138	Me		Intermediate 129			Tim Tec Overseas Stock Chembridge
139	Me		Intermediate 130	150	1.84	Tim Tec Overseas Stock
140	Me		Intermediate 131			T. Kohara et. Al; Tetrahedron Asymmetry, 1999, **10**, 4831-4840
141	Et		Intermediate 132			
142	Et		Intermediate 133			

143	Et		Intermediate 134			
144	Et		Intermediate 135			
145	Et		Intermediate 136			
75a	Et		Intermediate 50a			Tetrahedron Asymm.; 1999, **10**, 1579-1588
80a	Et		Intermediate 55a			
83a	Et		Intermediate 58a			

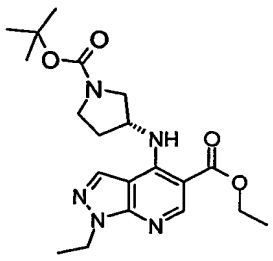
Intermediate 146: ethyl 4-[((3S)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-3-pyrrolidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



A solution of Intermediate 1 (680mg), DIPEA (2.3ml) and 1,1-dimethylethyl (3*S*)-3-amino-1-pyrrolidinecarboxylate (500mg) (e.g. available from Aldrich) in MeCN (15ml) was stirred and heated at reflux for 16h. The solvent was evaporated and the residue was partitioned between DCM and water. The organic phase was isolated by passage through a hydrophobic frit. The solvent was evaporated and the residue was purified on a 100g "flashmaster" cartridge (e.g. available from Jones Chromatography Ltd., United Kingdom), using a mixture of EtOAc and cyclohexane as the eluent, to give Intermediate 146 (720mg) as a solid. LCMS showed $MH^+ = 404$; $T_{RET} = 3.20$min.

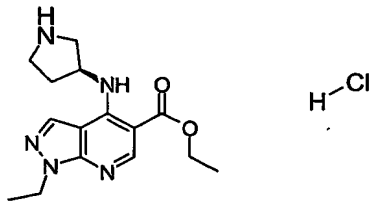
The following Intermediate 147 was prepared in a similar manner from Intermediate 1 and 1,1-dimethylethyl (3R)-3-amino-1-pyrrolidinecarboxylate (e.g. available from Aldrich):

Intermediate 147: ethyl 4-[((3R)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-3-pyrrolidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



LCMS showed $MH^+ = 404$; $T_{RET} = 3.20$min.

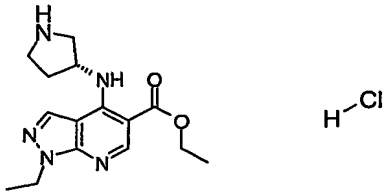
Intermediate 148: ethyl 1-ethyl-4-[(3*S*)-3-pyrrolidinylamino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate hydrochloride



A solution of Intermediate 146 (720mg) in 4.0M hydrogen chloride in dioxan (30ml) was stirred at 22°C for 3h. The solvent was evaporated to give Intermediate 148 (606mg) as a white solid. LCMS showed $MH^+ = 304$; $T_{RET} = 2.00$min.

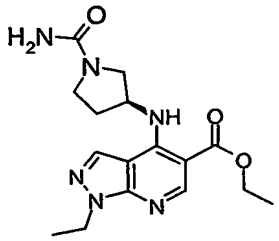
The following Intermediate 149 was prepared in a similar manner from Intermediate 147:

Intermediate 149: ethyl 1-ethyl-4-[(3R)-3-pyrrolidinylamino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate hydrochloride



LCMS showed $MH^+ = 304$; $T_{RET} = 2.00$min.

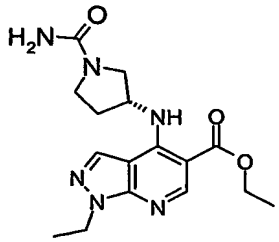
Intermediate 150: ethyl 4-{[(3*S*)-1-(aminocarbonyl)-3-pyrrolidinyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



A solution of Intermediate 148 (606mg) in DCM (30ml) was stirred and treated with DIPEA (1.15ml) followed by trimethylsilyl isocyanate (1.03ml). The reaction mixture was stirred at 22°C for 2h. The solution was washed with water. The aqueous phase was extracted with dichloromethane. The combined organics were passed through a hydrophobic frit and then concentrated to give Intermediate 150 (660mg) as a solid. LCMS showed $MH^+ = 347$; $T_{RET} = 2.40$min.

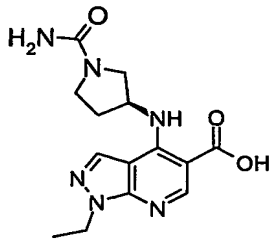
The following Intermediate 151 was prepared in a similar manner from Intermediate 149:

Intermediate 151: ethyl 4-{[(3*R*)-1-(aminocarbonyl)-3-pyrrolidinyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



LCMS showed $MH^+ = 347$; $T_{RET} = 2.40$min.

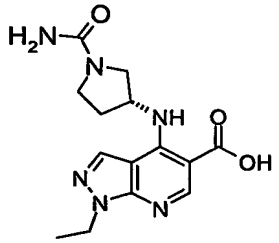
Intermediate 152: 4-{[(3*S*)-1-(aminocarbonyl)-3-pyrrolidinyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



A mixture of Intermediate 150 (660mg) and sodium hydroxide (300mg) in ethanol (15ml) and water (8ml) was stirred and heated at 60°C for 2h. The solvents were removed *in vacuo*. Water (8ml) was added to the residue and the resultant solution was acidified with 2M hydrochloric acid. The resultant suspension was filtered under suction. The residue was dried *in vacuo* to give Intermediate 152 (270mg) as a solid. LCMS showed MH^+ = 319; T_{RET} = 1.90min.

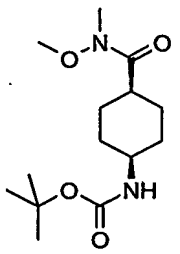
The following Intermediate 153 was prepared in a similar manner from Intermediate 151:

Intermediate 153: 4-{[(3R)-1-(aminocarbonyl)-3-pyrrolidinyl]amino}-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



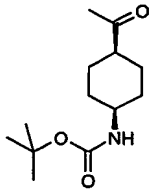
LCMS showed MH^+ = 319; T_{RET} = 1.90min.

Intermediate 154: 1,1-dimethylethyl (*cis*-4-{[methyl(methyloxy)amino]carbonyl}cyclohexyl)carbamate



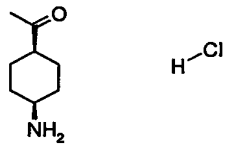
A solution of *cis*-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexanecarboxylic acid (1.0g) (e.g. available from Fluka), EDC (0.95g), HOBT (0.61g) and DIPEA (2.1ml) in THF (60ml) was stirred at 22°C for 30min then N,O-dimethylhydroxylamine hydrochloride (0.5g) was added. The reaction mixture was stirred for 7h. The solvent was removed and the residue was partitioned between DCM and saturated sodium bicarbonate solution. The organic phase was separated and the solvent was evaporated. The residue was applied to a 20g SPE cartridge. The cartridge was eluted with cyclohexane containing 10-50% EtOAc to give Intermediate 154 (768mg).

Intermediate 155: 1,1-dimethylethyl (*cis*-4-acetylcyclohexyl)carbamate



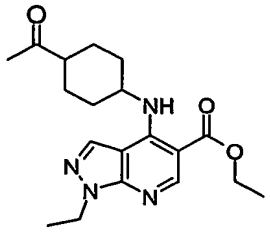
A solution of Intermediate 154 (768mg) in THF (25ml) was cooled to 0°C. A 3.0 Molar solution of methylmagnesium bromide in diethyl ether (2.2ml) was added rapidly dropwise over 5 min. The reaction mixture was stirred at 0-5°C for 3 hours. More 3.0 Molar methylmagnesium bromide in diethyl ether (0.9ml) was added. The reaction mixture was stirred at 0-5°C overnight. 1M hydrochloric acid (20ml) was added, dropwise. The reaction mixture was extracted with EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was applied to a 10g SPE cartridge. The cartridge was eluted with a (1:1) mixture of cyclohexane and EtOAc to give Intermediate 155 (340mg).

Intermediate 156: 1-(*cis*-4-aminocyclohexyl)ethanone hydrochloride



A stirred solution of Intermediate 155 (115mg) in dioxan (1ml) was treated with a 4M solution of hydrogen chloride in dioxan (240µl). The reaction mixture was stirred at room temperature for 4h then refrigerated overnight. The reaction mixture was concentrated *in vacuo* to give Intermediate 156 (72mg) as a solid.

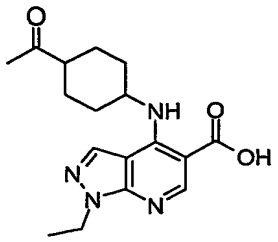
Intermediate 157: ethyl 4-[(4-acetylcyclohexyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (mixture of *cis* and *trans* isomers)



A solution of Intermediate 1 (93mg), Intermediate 156 (72mg) and DIPEA (0.32ml) in EtOH (10ml) was stirred and heated at reflux overnight. The solvent was evaporated and the residue was partitioned between DCM and saturated sodium bicarbonate solution. The organic phase was separated and concentrated. The residue was purified by mass directed

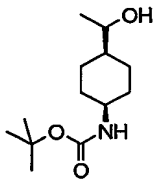
autoprep HPLC to give Intermediate 157 (102mg) as a mixture of *cis* and *trans* isomers. LCMS showed $MH^+ = 359$; $T_{RET} = 3.05$min.

Intermediate 158: 4-[(4-acetylcyclohexyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (mixture of cis and trans isomers)



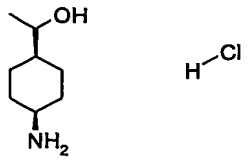
A solution of Intermediate 157 (102mg) and sodium hydroxide (45mg) in 95% aqueous EtOH was stirred and heated at 50°C overnight. The solvents were removed *in vacuo*. Water was added to the residue and the resultant solution was acidified with 2M hydrochloric acid. The resultant suspension was filtered. The residue was dried *in vacuo* to give Intermediate 158. The aqueous filtrate was extracted with EtOAc and DCM. The organic extracts were combined and concentrated to give a further quantity of Intermediate 158. The overall yield of Intermediate 158 was 70mg. LCMS showed $MH^+ = 331$; $T_{RET} = 2.46$min.

Intermediate 159: (RS)-1,1-dimethylethyl [*cis*-4-(1-hydroxyethyl)cyclohexyl]carbamate



A 1.5 Molar solution of diisobutylaluminium hydride in toluene (0.77ml) was added, dropwise, to a stirred solution of Intermediate 155 (112mg) in THF (5ml) at 0-5°C. The reaction mixture was stirred and warmed to room temperature overnight. More diisobutylaluminium hydride in toluene (0.31ml) was added. The reaction mixture was left at 22°C over the weekend., then treated with saturated sodium potassium tartrate solution (15ml). The mixture was stirred for 0.75h, then extracted with EtOAc. The combined extracts were washed with saturated sodium chloride solution, dried over $MgSO_4$ and concentrated. The residue was applied to a 2g SPE cartridge. The cartridge was eluted with cyclohexane containing 0-20% EtOAc to give Intermediate 159 (10mg).

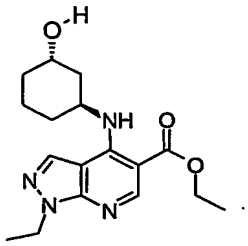
Intermediate 160: (RS)-1-(*cis*-4-aminocyclohexyl)ethanol hydrochloride



A solution of Intermediate 159 (10mg) in dioxan (0.5ml) was treated with a 4M solution of hydrogen chloride in dioxan (240µl). The reaction mixture was stirred at room temperature for 5h then left to stand overnight. The solvent was removed to give Intermediate 160 as a solid (7mg).

Intermediate 161: ethyl 1-ethyl-4-{[(1*SR*,3*SR*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate

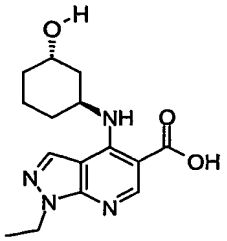
[*trans*-(3-hydroxycyclohex-1-yl)amino group, racemic]



A solution of 3-aminocyclohexanol (mixture of *cis* and *trans* isomers, 4.25g) (e.g. such a mixture is available from AB Chem, Inc., Canada; or see for example *J. Chem. Soc., Perkin Trans 1,* 1994, 537 for a 3.3 : 1 *cis* : *trans* mixture of 3-aminocyclohexanol), Intermediate 1 (7.8g) and DIPEA (25ml) in MeCN(50ml) and EtOH (5ml) was stirred and heated at reflux for 16h. The solvents were removed under reduced pressure and the residue was partitioned between DCM and water. The organic phase was concentrated and the residue was applied to a 100g SPE cartridge. The cartridge was eluted with a (1:2) mixture of EtOAc and cyclohexane to give Intermediate 161 (*trans* isomer: 326mg). LCMS showed $MH^+ = 333$; $T_{RET} = 2.90$min.

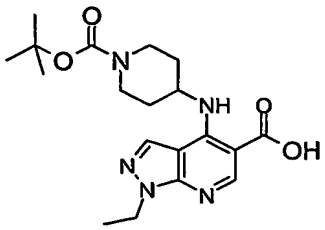
Intermediate 162: 1-ethyl-4-{[(*1SR,3SR*)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid

[*trans*-(3-hydroxycyclohex-1-yl)amino group, racemic]



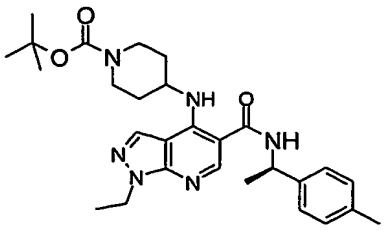
A mixture of Intermediate 161 (326mg) and sodium hydroxide (156mg) in water (2ml) and EtOH (4.6ml) was stirred and heated at 60°C for 5h then cooled and concentrated under reduced pressure. The residue was dissolved in water. The solution was acidified with 2M hydrochloric acid. The resultant suspension was filtered. The residue was dried *in vacuo* to give Intermediate 162 (270mg) as a white solid. LCMS showed $MH^+ = 305$; $T_{RET} = 2.21$min.

Intermediate 163: 4-[(1-{[(1,1-dimethylethyl)oxy]carbonyl}-4-piperidinyl)amino]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



A mixture of Intermediate 102 (750mg) and sodium hydroxide (290mg) in EtOH (20ml) and water (5ml) was stirred and heated at 50°C for 2.5h then cooled and concentrated under reduced pressure. A solution of the residue in water (20ml) was cooled to 0-5°C, with stirring, and acidified to pH=5 with 2M hydrochloric acid. The resultant solid suspension was filtered. The solid residue was washed with water and dried to give Intermediate 163 (575mg) as a white solid. LCMS showed $MH^+ = 390$; $T_{RET} = 2.86$min.

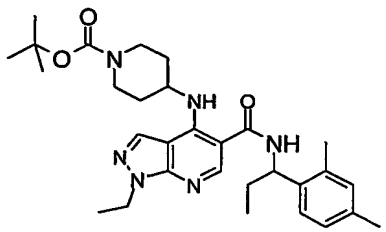
Intermediate 164: 1,1-dimethylethyl 4-{[1-ethyl-5-({[(1*R*)-1-(4-methylphenyl)ethyl]amino}carbonyl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl]amino}-1-piperidinecarboxylate



A solution of Intermediate 163 (100mg), EDC (54mg), HOBT (38mg) and DIPEA (0.11ml) in DMF (5ml) was added to [(1*R*)-1-(4-methylphenyl)ethyl]amine (38mg) (e.g. available from Lancaster). The solution was left to stand overnight. The solvent was evaporated. The residue was partitioned between DCM and saturated sodium bicarbonate solution. The organic phase was separated and evaporated. The residue was purified by passing through a 10g SPE cartridge, using a gradient of ethyl acetate and cyclohexane (0-100% EtOAc) as the eluent, to give Intermediate 164 (125mg). LCMS showed MH^+ = 507; T_{RET} = 3.85min.

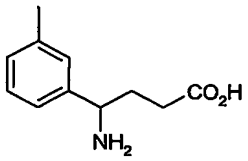
The following Intermediate 165 was prepared in a similar manner from Intermediate 163 and Intermediate 82:

Intermediate 165: 1,1-dimethylethyl 4-{[5-({[1-(2,4-dimethylphenyl)propyl]amino}carbonyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl]amino}-1-piperidinecarboxylate



(believed to be a mixture of isomers with the major isomer believed to have the (R)-stereochemistry at the benzylic carbon atom). LCMS showed MH^+ = 535; T_{RET} = 3.min.

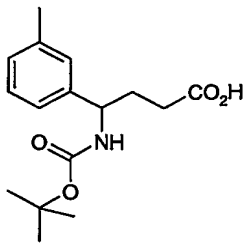
Intermediate 166: 4-Amino-4-(3-methylphenyl)butyric acid



Triethylamine (6.3g) was added to a cooled (0-5°C) solution of 4-(3-methylphenyl)-4-oxobutyric acid (e.g. available from Oakwood Products Inc., 8g) in DCM (100ml). Hydroxylamine hydrochloride (3.47g) was added slowly over 15 min. and the reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with 10% w/v sodium bicarbonate solution (2x75ml). The aqueous extracts were combined, washed with diethyl ether, acidified to pH = 2 with concentrated hydrochloric acid and extracted with ethyl acetate (3x100ml). The combined ethyl acetate extracts were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the intermediate oxime (8g). A solution of the oxime (4g) in methanol (50ml) was hydrogenated overnight at room temperature and 4-Kg hydrogen pressure, using 10% palladium on carbon as the catalyst. The reaction mixture was filtered through celite. The

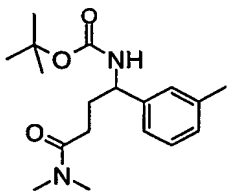
celite was washed with methanol and the combined filtrate and washings were concentrated. The residue was slurried in ethyl acetate. The resultant suspension was filtered. The residue was dried to give Intermediate 166 as a white solid (3.5g).

Intermediate 167: 4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-4-(3-methylphenyl)butanoic acid



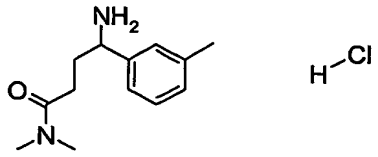
"BOC Anhydride" (di- tert-butyl carbonate, 4g) was added to a solution of Intermediate 166 (3.3g),and triethylamine (2.6g) in methanol (50ml) at 0-5°C. The reaction mixture was stirred at room temperature for 2 hours. 10% w/v Sodium bicarbonate solution (100ml) was added. The reaction mixture was washed with diethyl ether, acidified to pH = 3 with 20% w/v citric acid solution and extracted with ethyl acetate (3x50ml). The combined organics were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give Intermediate 167 (5.6g) as a white solid.

Intermediate 168: 1,1-dimethylethyl [4-(dimethylamino)-1-(3-methylphenyl)-4-oxobutyl]carbamate



A 30% w/v solution of dimethylamine in EtOH (0.46ml) was added to a stirred solution of Intermediate 167 (250mg), HOBT (126mg), EDC (180mg) and DIPEA (0.37ml) in MeCN. The reaction mixture was stirred for 24h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and 0.5M sodium bicarbonate solution. The organic phase was washed with saturated brine and dried by passing through a 10g cartridge of $MgSO_4$ under suction. The solution was concentrated *in vacuo*. The residue was purified by passing through a 10g SPE cartridge, using a (1:1) mixture of cyclohexane and EtOAc as the eluent, to give Intermediate 168 (109mg) as a white solid. LCMS showed $MH^+ = 321$; $T_{RET} = 2.88$min.

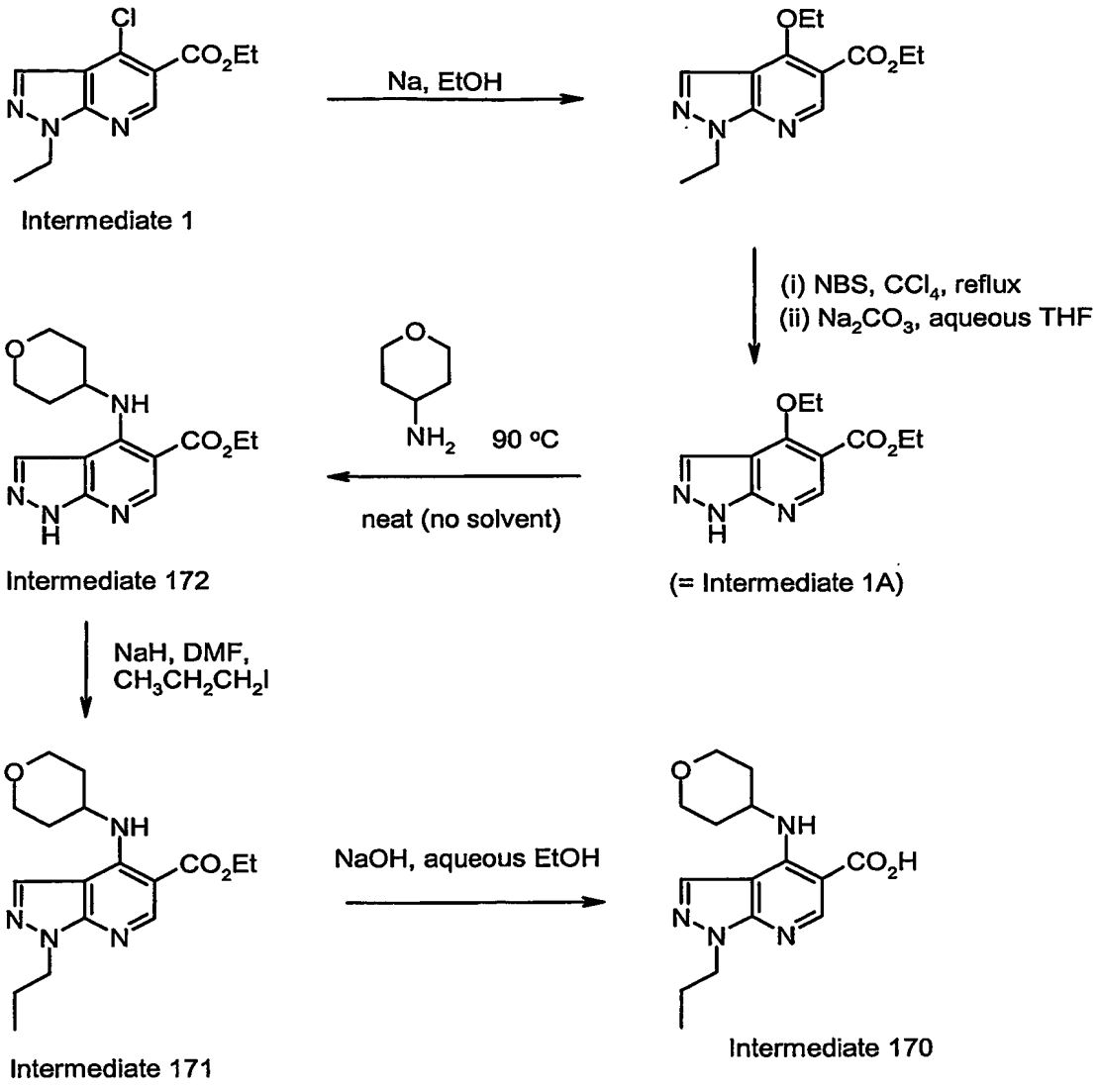
Intermediate 169: 4-amino-*N*,*N*-dimethyl-4-(3-methylphenyl)butanamide hydrochloride



Intermediate 168 (108mg) was treated with a 4M solution of hydrogen chloride in dioxan (2ml). The reaction mixture was stirred for 6.5h then concentrated *in vacuo*. The residue was triturated in diethyl ether. The diethyl ether was decanted. The residue was purified by passing through a 5g SPE silica cartridge, using a gradient of 10-50% methanol in ethyl acetate as the eluent, to give Intermediate 169 (56mg) as a white solid. LCMS showed $MH^+ = 221$; $T_{RET} = 1.74$min.

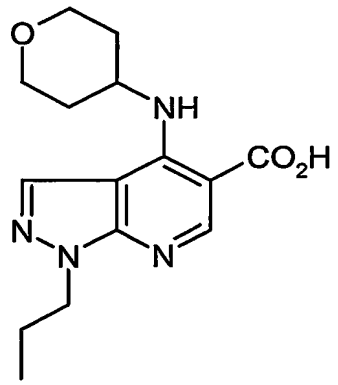
Intermediate 170:

Intermediate 170 can be synthesised according to the following reaction scheme:



The final step in the above Intermediate 170 reaction scheme can optionally be performed as follows:

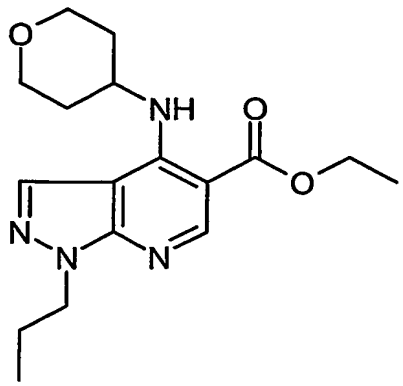
Intermediate 170: 1-n-Propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



Optional synthesis: 2M-Sodium hydroxide solution (0.7ml) was added to a stirred suspension of the corresponding ethyl ester (Intermediate 171) (0.23g) in ethanol (5ml) and water (1.5ml). After stirring overnight at room temperature, a further quantity of 2M-sodium hydroxide solution (0.7ml) was added, and the reaction mixture was heated at 43 °C for 2.5h. The reaction solution was concentrated, diluted with water (5ml) and acidified with 2M-hydrochloric acid. The resulting precipitate was collected by filtration, washed with water and dried to give Intermediate 170 as a white solid (0.14g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.42$min.

The penultimate step in the above Intermediate 170 reaction scheme (to make Intermediate 171) can optionally be performed as follows:

Intermediate 171: Ethyl 1-n-propyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate

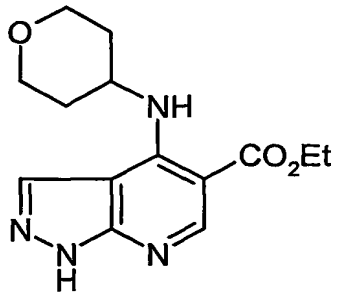


Optional synthesis: Sodium hydride (0.067g, 60% dispersion in oil) was added to a stirred solution of Intermediate 172 (0.47g) in DMF (19ml), followed by n-propyl iodide (0.17ml). The mixture was stirred at 23 °C for 16 hours, then concentrated, diluted with chloroform (30ml) and washed with 1:1 water:brine solution (30ml), separated and the organic layer concentrated. The residue was purified on a SPE catridge (silica, 10g)

eluting with 10ml volumes of dichloromethane, 1:1 diethyl ether : cyclohexane, and diethyl ether. The combined 1:1 diethyl ether : cyclohexane, and diethyl ether, fractions were concentrated to give Intermediate 171 as a clear gum (0.23g). LCMS showed MH^+ = 333; T_{RET} = 3.14min.

The ante-penultimate step in the above Intermediate 170 reaction scheme (to make Intermediate 172) can optionally be performed as follows:

Intermediate 172: Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



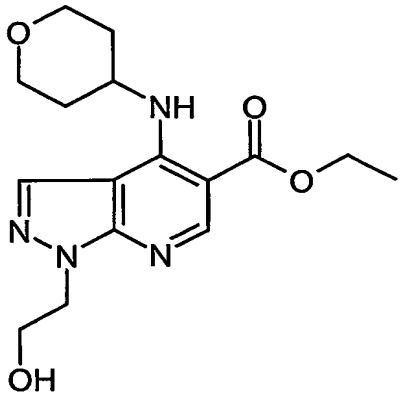
Optional synthesis no. 1:

Intermediate 1A (0.035g) was placed in a Reactivial™ and treated with 4-aminotetrahydropyran (0.05ml). The mixture was heated at 90°C for 1.5h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated. The crude product was purified by mass directed autoprep HPLC to afford Intermediate 172 as an off-white solid (0.011g). LCMS showed MH^+= 291; T_{RET} = 2.08 min.

Alternative optional synthesis no. 2:

Intermediate 1A (2g) was suspended in 4-aminotetrahydropyran (2g), and the mixture was heated at 90 °C for 6h. The residual mixture was allowed to cool to room temperature and partitioned between chloroform (50ml) and water (50ml). The phases were separated and the organic phase was evaporated to dryness. The residue was triturated with Et_2O (30ml) and the insoluble solid was collected and dried to afford Intermediate 172 as a cream solid (2.24g). LCMS showed MH^+= 291; T_{RET} = 2.19min.

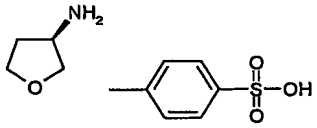
Intermediate 173: **Ethyl 1-(2-hydroxyethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate**



2-Bromoethanol (0.008ml) was added to a solution of Intermediate 172 (0.03g) in anhydrous DMF (1.5ml), with 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (polymer bound, 2.3mmol/g loading, 0.045g). The mixture was shaken at 23 °C for 16 hours, then the solution drained from the resin, and the resin was washed with DMF. The combined organics were concentrated, and the residue purified on a SPE cartridge (silica, 1g) eluting with 70-100% ethyl acetate in cyclohexane. The combined fractions were concentrated to give Intermediate 173 as a white solid (0.011g). LCMS showed MH^+ =335; T_{RET} = 2.47min.

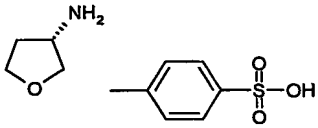
Intermediate 175: **(R)-(+)-3-Amino tetrahydrofuran 4-toluenesulphonate**

Commercially available from Fluka Chemie AG, Germany (CAS 111769-27-8)



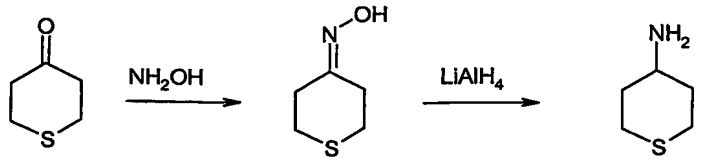
Intermediate 176: **(S)-(-)-3-Amino tetrahydrofuran 4-toluenesulphonate**

Commercially available from E. Merck, Germany; or from E. Merck (Merck Ltd), Hunter Boulevard, Magna Park, Lutterworth, Leicestershire LE17 4XN, United Kingdom (CAS 104530-80-5)



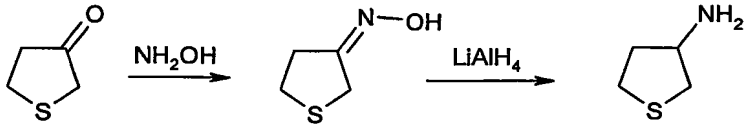
Intermediate 177: **Tetrahydro-2H-thiopyran-4-amine**

This can be prepared from commercially available tetrahydrothiopyran-4-one as described by Subramanian et. al., *J. Org. Chem.*, 1981, 46, 4376-4383. Subsequent preparation of the hydrochloride salt can be achieved by conventional means.



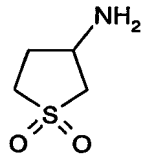
Intermediate 178: Tetrahydro-3-thiopheneamine

This can be prepared in an analogous manner to Intermediate 177 from commercially available tetrahydrothiophene-4-one. The oxime formation is described by Grigg et.al., *Tetrahedron*, 1991, 47, 4477-4494 and the oxime reduction by Unterhalt et. al., *Arch. Pharm.*, 1990, 317-318.



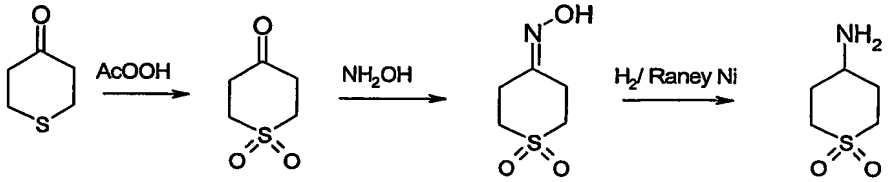
Intermediate 179: Tetrahydro-3-thiopheneamine 1,1-dioxide hydrochloride

Commercially available from Sigma Aldrich Library of Rare Chemicals (SALOR) (CAS-6338-70-1). Preparation of the hydrochloride salt of the amine can be achieved by conventional means.

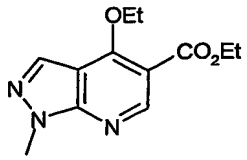


Intermediate 180: Tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride

This can be prepared in an analogous manner to Intermediate 177 from commercially available tetrahydrothiopyran-4-one. Oxidation to 1,1-dioxo-tetrahydro-1λ^6-thiopyran-4-one is described by Rule et. al., in *J. Org. Chem.*, 1995, 60, 1665-1673. Oxime formation is described by Truce et.al., in *J. Org. Chem.*, 1957, 617, 620 and oxime reduction by Barkenbus et. al., *J. Am. Chem. Soc.*, 1955, 77, 3866. Subsequent preparation of the hydrochloride salt of the amine can be achieved by conventional means.

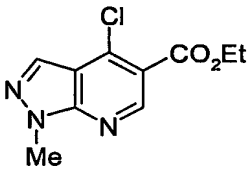


Intermediate 181: Ethyl 1-methyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



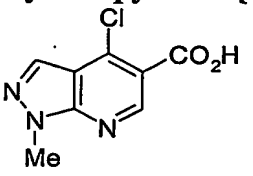
A mixture of Intermediate 1A (0.47g) and anhydrous potassium carbonate (0.83g) (previously dried by heating at 100°C) in anhydrous dimethylformamide (DMF) (4ml) was treated with iodomethane (0.26ml) and stirred vigorously for 3h. The mixture was then filtered and the filtrate concentrated in vacuo to afford a residual oil, which was partitioned between dichloromethane (DCM) (25ml) and water (25ml). The layers were separated and the aqueous phase was extracted with further DCM (2x25ml). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated to an orange solid which was applied to an SPE cartridge (silica, 20g). The cartridge was eluted sequentially with EtOAc : petrol (1:4, 1:2 and 1:1), then chloroform : methanol (49:1, 19:1 and 9:1). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 181 (0.165g). LCMS showed MH^+= 250; T_{RET} = 2.59 min.

Intermediate 182: Ethyl 4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



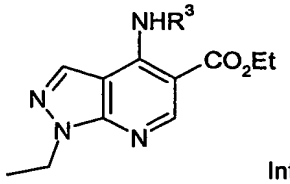
A mixture of 5-amino-1-methyl pyrazole (4.0g) and diethylethoxymethylene malonate (9.16ml) was heated at 150°C under Dean Stark conditions for 5h. Phosphorous oxychloride (55ml) was carefully added to the mixture and the resulting solution heated at 130°C under reflux for 18h. The mixture was concentrated in vacuo, then the residual oil cooled in an ice bath and treated carefully with water (100ml) (caution: exotherm). The resulting mixture was extracted with DCM (3x100ml) and the combined organic extracts were dried over anhydrous sodium sulphate and concentrated in vacuo. The residual solid was purified by Biotage chromatography (silica, 90g), eluting with Et_20 : petrol (1:3). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 182 (4.82g). LCMS showed MH^+ = 240; T_{RET} = 2.98min

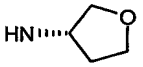
Intermediate 183: 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 182 (4.0g) in dioxane (30ml) was treated with potassium hydroxide (7.54g) as a solution in water (20ml). The mixture was stirred for 16h, then diluted with water (150ml) and acidified to pH 3 with 5M aqueous hydrochloric acid. The mixture was stirred in an ice bath for 15min, then collected by filtration, washed with ice-cold water and dried in vacuo over phosphorous pentoxide to afford Intermediate 183 as a white solid (2.83g). LCMS showed $MH^+ = 212$; $T_{RET} = 2.26$min.

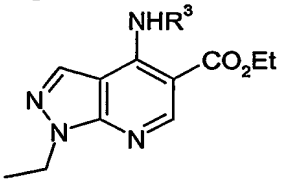
Intermediate 184: Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

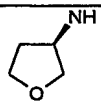
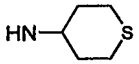


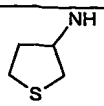
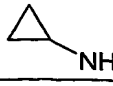
Intermediate 184 NHR^3 = 

Intermediate 1 (0.05g) and (S)-(-)-3-aminotetrahydrofuran 4-toluenesulphonate (Intermediate 176) (0.052g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:16 then, 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 184 (0.052g). LCMS showed $MH^+ = 305$; $T_{RET} = 2.70$min.

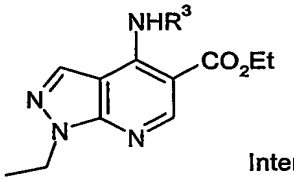
Similarly prepared were the following:

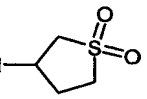


	NHR^3	Amine Reagent	MH^+ ion	T_{RET}(min)
Intermediate 185		(R)-(+)-3-Aminotetrahydrofuran 4-toluenesulphonate (Intermediate 175)	305	2.73
Intermediate 186		Intermediate 177	335	3.21

Intermediate 187		Intermediate 178	321	3.10
Intermediate 188		Cyclopropylamine	275	2.98

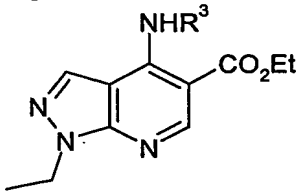
Intermediate 189: Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

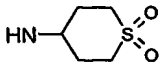


Intermediate 189 NHR^3 = 

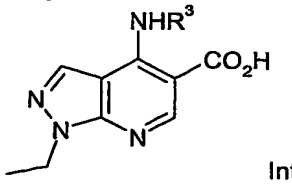
Intermediate 1 (0.05g) and Intermediate 179 (0.027g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:8 then 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 189 (0.045g) as a mixture of enantiomers. LCMS showed $MH^+ = 353$; $T_{RET} = 2.60$min.

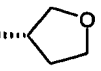
Similarly prepared was the following:



	NHR^3	Amine Reagent	MH^+ ion	T_{RET}(min)
Intermediate 190		Intermediate 180	367	2.64

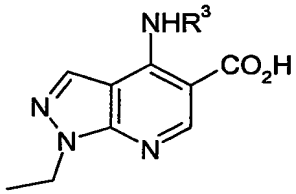
Intermediate 191: 1-Ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

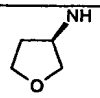
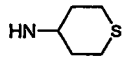
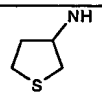
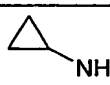
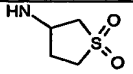
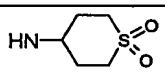


Intermediate 191 NHR^3 = 

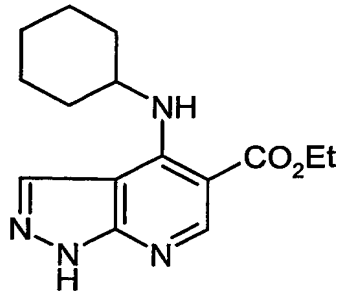
A solution of Intermediate 184 (0.037g) in ethanol : water (95:5, 3ml) was treated with sodium hydroxide (0.019g). The mixture was heated at 50°C for 16h, then concentrated in vacuo. The residue was dissolved in water (1.5ml) and acidified to pH 4 with acetic acid. The resultant white solid precipitate was removed by filtration and dried under vacuum. The filtrate was extracted with ethyl acetate and the organic layer collected and concentrated in vacuo to afford a further portion of white solid. The two solids were combined to afford Intermediate 191 (0.033g). LCMS showed MH^+ = 277; T_{RET} = 2.05 min.

Similarly prepared were the following:



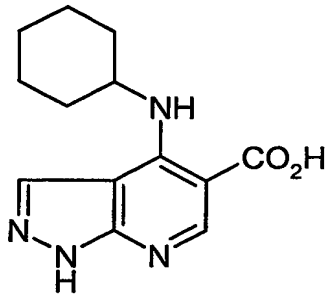
	NHR^3	Starting material	MH^+ ion	T_{RET}(min)
Intermediate 192		Intermediate 185	277	2.05
Intermediate 193		Intermediate 186	307	2.40
Intermediate 194		Intermediate 187	293	2.59
Intermediate 195		Intermediate 188	247	2.24
Intermediate 196		Intermediate 189	325	2.05
Intermediate 197		Intermediate 190	339	2.05

Intermediate 198: Ethyl 4-(cyclohexylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



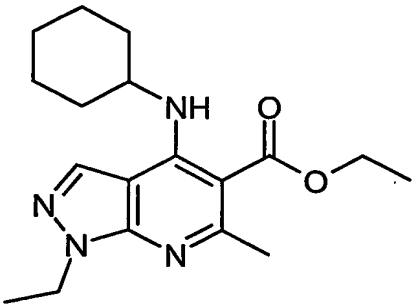
Intermediate 1A (0.69g) was suspended in cyclohexylamine (1.01ml), and the mixture was heated at 90 °C for 3h. The residual mixture was allowed to cool to room temperature and partitioned between chloroform (25ml) and water (25ml). The phases were separated and the organic phase was evaporated to dryness. The residue was triturated with Et_2O (25ml) and the insoluble solid was collected and dried to afford Intermediate 198 as a beige solid (0.58g). LCMS showed MH^+=289; T_{RET} = 2.91min.

Intermediate 199: 4-(Cyclohexylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



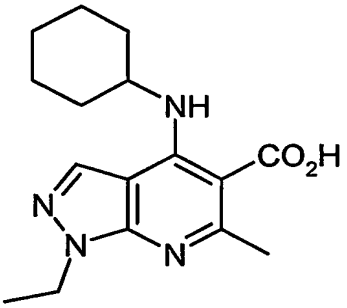
2M-Sodium hydroxide solution (0.5ml) was added to a stirred suspension of Intermediate 198 (0.2g) in dioxan (4ml) and water (0.5ml). After stirring overnight at room temperature, the reaction mixture was heated at 40 °C for 8h. A further quantity of 2M-sodium hydroxide solution (1.5ml) was added, and the reaction mixture was heated at 40 °C for 48h. The reaction solution was concentrated, diluted with water (10ml) and acidified with glacial acetic acid. The resulting precipitate was collected by filtration, washed with water and dried to give Intermediate 199 (0.18g). LCMS showed MH^+ = 261; T_{RET} = 2.09min.

Intermediate 200: **Ethyl 4-(cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate**



Cyclohexylamine (0.149g, 1.5mmol) was added to a mixture of Intermediate 10 (0.201g, 0.75mmol) and N,N-diisopropylethylamine (0.65ml, 3.73mmol) in acetonitrile (3ml). The resulting mixture was heated at 85 °C for 40 hours. Volatiles were removed *in vacuo* and the residue was dissolved in chloroform (1.5ml) and applied to a SPE cartridge (silica, 5g). The cartridge was eluted successively with Et_2O, EtOAc and MeOH. Fractions containing the desired product were combined and concentrated *in vacuo* to afford Intermediate 200 (0.128g). LCMS showed $MH^+ = 331$; $T_{RET} = 3.64$min.

Intermediate 201: **4-(Cyclohexylamino)-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid**

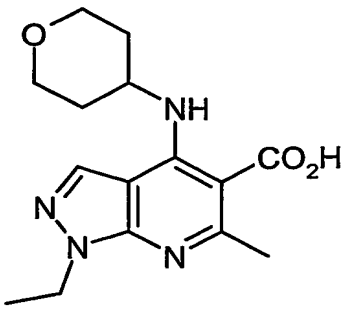


2M-Sodium hydroxide solution (0.39ml, 0.78mmol) was added to the corresponding ethyl ester (Intermediate 200) (0.128g, 0.39mmol) in ethanol (1.5ml), and the mixture was heated at 50 °C for 16 hours. The reaction mixture was concentrated, and the resulting aqueous solution was neutralised with 2M-hydrochloric acid to precipitate a solid which was collected by filtration. The filtrate was applied to an OASIS ® hydrophilic-lipophilic balance (HLB) Extraction cartridge * (1g) which was eluted with water followed by methanol. Evaporation of the methanol fraction gave a solid which was combined with the initial precipitated solid to afford Intermediate 201 (0.083g) as a white solid, presumed to be the carboxylic acid.

* OASIS ® HLB Extraction cartridges are available from Waters Corporation, 34 Maple Street, Milford, MA 01757, USA. The cartridges include a column containing a copolymer sorbent having a HLB such that when an aqueous solution is eluted through the column, the solute is absorbed or adsorbed into or onto the sorbent, and such that

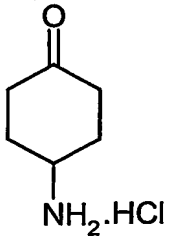
when organic solvent (e.g. methanol) is eluted the solute is released as an organic (e.g. methanol) solution. This is a way to separate the solute from aqueous solvent.

Intermediate 202: 1-Ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid



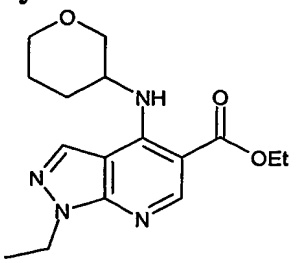
2M-Sodium hydroxide solution (0.75ml, 1.5mmol) was added to Intermediate 11 (0.248g, 0.75mmol) in ethanol (2ml), and the mixture was heated at reflux for 16 hours. The reaction mixture was concentrated, diluted with water (1ml) and acidified with 2M-hydrochloric acid (0.75ml) to precipitate a solid which was collected by filtration to afford Intermediate 202 (0.168g). LCMS showed $MH^+ = 305$; $T_{RET} = 1.86$min.

Intermediate 203: 4-Aminocyclohexanone hydrochloride



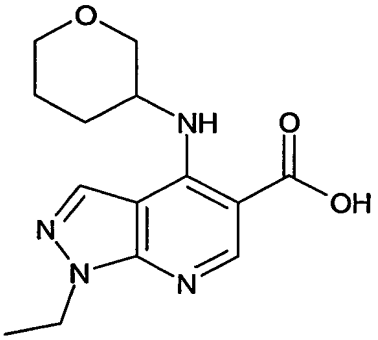
A solution of hydrogen chloride in dioxan (0.5ml, 2.0mmol, 4M) was added to a stirred solution of *tert*-butyl 4-oxocyclohexylcarbamate (0.043g, 0.20mmol, commercially available from AstaTech Inc., Philadelphia, USA) in dioxan (0.5ml) and the mixture was stirred at room temperature. After 1h, the reaction mixture was evaporated to give Intermediate 203 as a cream solid (34mg). ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) 8.09 (br. s, 3H), 3.51 (tt, 11, 3.5Hz, 1H), 2.45 (m, 2H, partially obscured), 2.29 (m, 2H), 2.16 (m, 2H), 1.76 (m, 2H).

Intermediate 204: Ethyl 1-ethyl-4-(tetrahydro-2*H*-pyran-3-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate



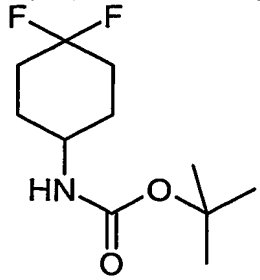
Intermediate 1 (0.76g, 3.0mmol)) was dissolved in acetonitrile (10ml). Tetrahydro-2*H*-pyran-3-amine hydrochloride (0.5g, 3.6mmol, *Anales De Quimica*, 1988, **84**, 148) and *N,N*-diisopropylethylamine (3.14ml, 18.0mmol) were added and the mixture was stirred at 85°C for 24h. After 24h a further portion of tetrahydro-2*H*-pyran-3-amine hydrochloride (0.14g, 1.02mmol) was added and stirring was continued at 85°C. After a further 8h, the mixture was concentrated *in vacuo*. The residue was partitioned between DCM (20ml) and water (12ml). The layers were separated and the aqueous layer was extracted with further DCM (12ml). The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to give a brown solid which was purified on a SPE cartridge (silica, 20g) eluting with a gradient of ethyl acetate:cyclohexane (1:16, 1:8, 1:4, 1:2, 1:1, 1:0). Fractions containing the desired material were combined and evaporated to afford Intermediate 204 (0.89g). LCMS showed $MH^+ = 319$; $T_{RET} = 2.92$ min.

Intermediate 205: 1-Ethyl-4-(tetrahydro-2H-pyran-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 204 (0.89g, 2.79mmol) in ethanol (16.7ml) was treated with sodium hydroxide (0.47g, 11.7mmol) as a solution in water (3.1ml). The mixture was stirred at 50 °C. After 12h, the reaction mixture was concentrated *in vacuo* to give a residual oil which was dissolved in water (16ml), then cooled and acidified to pH 3 with 2M hydrochloric acid. After stirring at 0°C for 30min, the resulting precipitate was collected by filtration, washed with cooled water (2ml) and dried in vacuo to afford Intermediate 205 as a white solid (0.73g). LCMS showed $MH^+ = 291$; $T_{RET} = 2.19$min.

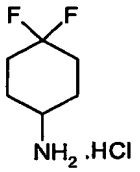
Intermediate 206: 1,1-Dimethylethyl (4,4-difluorocyclohexyl)carbamate



(Diethylamino)sulphur trifluoride (DAST), (0.06ml, 0.47mmol), was added to a stirred solution of 1,1-dimethylethyl(4-oxocyclohexyl)carbamate, (250mg, 1.17mmol,

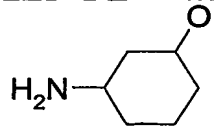
commercially available from AstaTech Inc., Philadelphia, USA) in anhydrous dichloromethane (5ml) and the mixture was stirred under nitrogen at 20°C. After 22h, the reaction mixture was cooled to 0°C, treated with saturated sodium hydrogen carbonate solution (4ml), and then allowed to warm to ambient temperature. The phases were separated by passage through a hydrophobic frit and the aqueous phase was further extracted with DCM (5ml). The combined organic phases were concentrated in vacuo to give an orange solid (369mg) which was further purified by chromatography using a SPE cartridge (silica, 10g), eluting with DCM to afford **Intermediate 206** (140mg) containing 20% of **1,1-dimethylethyl (4-fluoro-3-cyclohexen-1-yl)carbamate.** ^{1}H NMR (400MHz in $CDCl_3$, 27°C, δppm).
Minor component: δ5.11 (dm, 16Hz, 1H), 4.56 (br, 1H), 3.80 (br, 1H) 2.45-1.45 (m's, 6H excess), 1.43 (s, 9H). Major component: δ4.43 (br, 1H), 3.58 (br, 1H), 2.45-1.45 (m's, 8H excess), 1.45 (s, 9H).

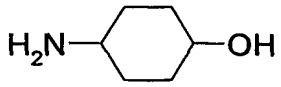
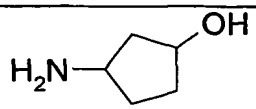
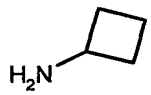
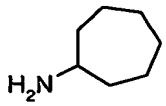
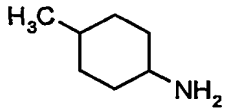
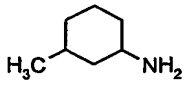
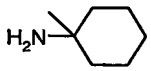
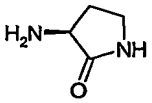
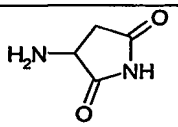
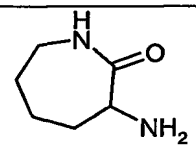
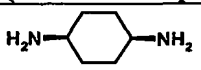
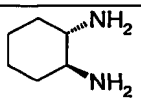
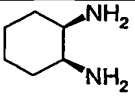
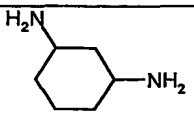
Intermediate 207: (4,4-Difluorocyclohexyl)amine hydrochloride

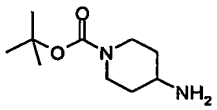
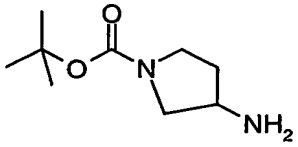
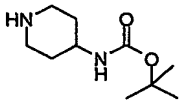
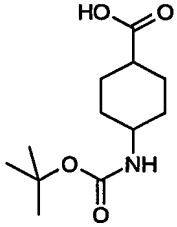
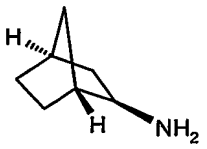
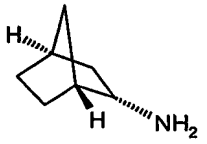


A solution of hydrogen chloride in dioxane (4M, 1.6ml) was added at 20°C to a stirred solution of Intermediate 206 (140mg, 0.6mmol), in dioxane (1.6ml). After 3h, the reaction mixture was concentrated in vacuo to afford **Intermediate 207** (96.5mg) containing **4-fluoro-3-cyclohexen-1-amine.** ^{1}H NMR (400MHz in d_6-DMSO, 27°C, δppm) Minor component: δ8.22 (br, 3H excess), 5.18 (dm, 16Hz, 1H), 3.28-3.13 (m, 1H excess), 2.41-1.53 (m's, 6H excess). Major component: δ8.22 (br, 3H excess), 3.28-3.13 (m, 1H excess), 2.41-1.53 (m's, 8H excess). Impurities are also present.

Intermediates 208 to 229: different types of R^3NH_2

Intermediate Number	R^3NH_2	One Possible Source of, and/or a Reference to, R^3NH_2
208		AB Chem, Inc., Canada (mixture of *cis* and *trans*); or *J. Chem. Soc., Perkin Trans. 1*, 1994, 537
208A	as Intermediate 208, but racemic *cis*-isomer, i.e. racemic *cis*-(3-hydroxy-	*J. Chem. Soc., Perkin Trans 1*, 1994, 537 (discloses a 3.3 : 1 *cis* :

	cyclohex-1-yl)-amine	*trans* mixture)
209		Aldrich; or TCI-America
210		US 4219660
211		Aldrich
212		Aldrich
213		Aldrich
214		Pfaltz-Bauer
215		*J. Org. Chem.*, 1985, 50(11), 1859
216		WO 99/12933
217		EP 1188744
218	 (3-Aminoazepan-2-one)	Sigma-Aldrich Company Ltd
219 *		*J. Med. Chem.*, 1994, 37(17), 2360
220 *		Aldrich
221 *		Aldrich
222 *		Aldrich
223 *		Peakdale Molecular Ltd

224	 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate	AstaTech
225		
226	 1,1-dimethylethyl 4-piperidinylcarbamate	Syngene or AstaTech
227	 4-({[(1,1-dimethylethyl)oxy]carbon-yl}amino)cyclohexane carboxylic acid	Fluka
228		Aldrich
229		Aldrich

* For R^3NH_2 in Intermediates 219-223, R^3NH_2 is the *cis* or *trans* isomer, if shown. For Intermediates 221-223, R^3NH_2 is usually the 3-amino- or 2-amino- cyclohex-1-ylamine in a racemic form.

Many of Intermediates 208 to 229, either as they are or after deprotection, protection and/or functional group interconversion(s), can optionally be used as R^3NH_2 amines in the preparation of compounds of formula (I) or precursors thereto, e.g. as described in

Processes A or B and/or Process D hereinabove; optionally followed by deprotection, protection and/or functional group interconversion(s) e.g. in the 4-(R^3NH) group of the pyrazolopyridine compound prepared.

5

Table of Examples

Example Number	Name
1	1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
2	1-ethyl-*N*-(1-methyl-1-phenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
3	1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
4	*N*-(diphenylmethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
5	1-ethyl-*N*-[1-(3-pyridinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
6	1-ethyl-*N*-[(1*S*)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
7	1-ethyl-*N*-[(1*S*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
8	1-ethyl-*N*-[(1*R*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
9	1-ethyl-*N*-[1-methyl-1-(4-pyridinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
10	1-ethyl-*N*-[(1*R*)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
11	*N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
12	1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
13	1-ethyl-*N*-(3-hydroxy-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
14	1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
15	*N*-[2-(dimethylamino)-1-phenylethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
16	1-ethyl-*N*-[1-phenyl-2-(1-pyrrolidinyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
17	1-ethyl-*N*-[1-(hydroxymethyl)-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
18	1-ethyl-*N*-{1-[4-(propyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide
19	methyl 3-({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-phenylpropanoate

20 1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

21 *N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

22 ethyl ({[1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)(phenyl)acetate

23 1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

24 1-ethyl-*N*-[(1*S*)-2-(methyloxy)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

25 *N*-[(1*R*)-2-amino-2-oxo-1-phenylethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

26 1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

27 1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

28 1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

29 1-ethyl-*N*-[(1*R*)-2-(methyloxy)-1-phenylethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

30 1-ethyl-*N*-(2-hydroxy-1,1-diphenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

31 *N*-[1-(3-cyanophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

32 *N*-[cyano(phenyl)methyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

33 *N*-{cyclopropyl[4-(methyloxy)phenyl]methyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

34 1-ethyl-*N*-[1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

35 *N*-(1,2-diphenylethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

36 1-ethyl-*N*-{1-[4-(methyloxy)phenyl]butyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

37 1-ethyl-*N*-[(1*R*)-1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

38 1-ethyl-*N*-[(1*S*)-1-(1-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

39 *N*-[1-(aminocarbonyl)-1-phenylpropyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

40 1-ethyl-*N*-(1-phenylcyclopentyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

41 1-ethyl-*N*-(4-phenyltetrahydro-2*H*-pyran-4-yl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

42 1-ethyl-*N*-(1-phenylcyclopropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

43 *N*-{1-[4-(cyclohexyloxy)-3-methylphenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

44 *N*-{1-[3-(cyclohexyloxy)-4-(methyloxy)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

45 *N*-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

46 *N*-{1-[4-(cyclohexyloxy)-3-hydroxyphenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

47 *N*-{1-[4-(cyclopentyloxy)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

48 1-ethyl-*N*-[1-(4-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

49 *N*-{1-[4-(1,1-dimethylethyl)phenyl]cycloheptyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

50 *N*-[1-(4-bromophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

51 1-ethyl-*N*-[(1*S*)-1-(4-iodophenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

52 *N*-{1-[4-(aminosulfonyl)phenyl]ethyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

53 1-ethyl-*N*-(1-methyl-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

54 *N*-[1-(1,3-benzodioxol-5-yl)cyclohexyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

55 1-ethyl-*N*-{1-[4-(methyloxy)phenyl]cyclohexyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

56 1-ethyl-*N*-[1-(4-fluorophenyl)cyclohexyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

57 *N*-[1-(3-chlorophenyl)cyclopentyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

58 *N*-[1-(2-chlorophenyl)cyclopentyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

59 *N*-{1-[4-(1,1-dimethylethyl)phenyl]cyclohexyl}-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

60 1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

61 *N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-

ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

62 1-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-phenylpropyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

63 1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

64 1-ethyl-*N*-{(1*S*)-1-[4-(methyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

65 1-ethyl-*N*-(1-phenylhexyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

66 1-ethyl-*N*-(1-phenylpentyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

67 1-ethyl-*N*-(2-methyl-1-phenylpropyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

68 1-ethyl-*N*-(1-phenylbutyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

69 1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-(2,2,2-trifluoro-1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

70 *N*-[cyclopropyl(phenyl)methyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

71 1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

72 *N*-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

73 1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

74 1-ethyl-*N*-(1-phenylethyl)-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

75 *N*-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

76 *N*-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

77 *N*-[1-(3,4-dichlorophenyl)-2-hydroxyethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

78 1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

79 1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

80 *N*-[1-(4-bromophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

81 1-ethyl-*N*-{1-[4-(propyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

82 *N*-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-

ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

83 1-ethyl-*N*-[1-(4-methylphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

84 1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

85 1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

86 *N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

87 1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

88 1-ethyl-*N*-[1-(2-methylphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

89 1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

90 *N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

91 1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

92 *N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

93 *N*-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

94 *N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

95 *N*-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

96 *N*-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

97 *N*-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

98 *N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

99 *N*-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

100 *N*-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

101 1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

102 *N*-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

103 1-ethyl-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

104 *N*-[1-(4-bromophenyl)-2,2,2-trifluoroethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

105 1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-*N*-{2,2,2-trifluoro-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

106 4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

107 4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

108 4-(cyclohexylamino)-*N*-(diphenylmethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

109 4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

110 ethyl ({[4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)(phenyl)acetate

111 *N*-[1-(4-chlorophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

112 4-(cyclohexylamino)-1-ethyl-*N*-(1-methyl-1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

113 4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

114 *N*-[1-(4-chlorophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

115 4-(cyclohexylamino)-*N*-(1,2-diphenylethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

116 4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

117 methyl 3-({[4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyl}amino)-3-phenylpropanoate

118 4-(cyclohexylamino)-1-ethyl-*N*-[1-(hydroxymethyl)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

119 4-(cyclohexylamino)-1-ethyl-*N*-(3-hydroxy-1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

120 4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

121 4-(cyclohexylamino)-1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

122 4-(cyclohexylamino)-1-ethyl-*N*-[1-phenyl-2-(1-pyrrolidinyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

123 4-(cyclohexylamino)-*N*-[2-(dimethylamino)-1-phenylethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

124 4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-2-(methyloxy)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

125 *N*-[(1*R*)-2-amino-2-oxo-1-phenylethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

126 4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

127 4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

128 4-(cyclohexylamino)-1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

129 4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-2-(methyloxy)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

130 4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

131 4-(cyclohexylamino)-1-ethyl-*N*-[(1*S*)-1-(1-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

132 4-(cyclohexylamino)-1-ethyl-*N*-[phenyl(4-phenyl-1,3-thiazol-2-yl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

133 *N*-[cyano(phenyl)methyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

134 4-(cyclohexylamino)-1-ethyl-*N*-[1-(1-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

135 4-(cyclohexylamino)-1-ethyl-*N*-(2-hydroxy-1,1-diphenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

136 4-(cyclohexylamino)-1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

137 4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

138 4-(cyclohexylamino)-*N*-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

139 4-(cyclohexylamino)-1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

140 4-(cyclohexylamino)-1-ethyl-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

141 *N*-[(1*R*)-1-(4-bromophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

142 4-(cyclohexylamino)-*N*-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

143 4-(cyclohexylamino)-1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

144 4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

145 *N*-[1-(4-bromophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

146 4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

147 4-(cyclohexylamino)-*N*-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

148 4-(cyclohexylamino)-1-ethyl-*N*-[1-(4-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

149 4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

150 4-(cyclohexylamino)-1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

151 4-(cyclohexylamino)-*N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

152 4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

153 4-(cyclohexylamino)-1-ethyl-*N*-[1-(2-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

154 4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

155 4-(cyclohexylamino)-*N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

156 4-(cyclohexylamino)-1-ethyl-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

157 4-(cyclohexylamino)-*N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

158 4-(cyclohexylamino)-*N*-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

159 4-(cyclohexylamino)-*N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

160 *N*-[1-(4-chloro-2-fluorophenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

161 *N*-[1-(3-chloro-4-methylphenyl)ethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

162 4-(cyclohexylamino)-*N*-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

163 4-(cyclohexylamino)-*N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

164 *N*-[1-(4-chloro-2-fluorophenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

165 *N*-[1-(3-chloro-4-methylphenyl)propyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

166 4-(cyclohexylamino)-1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

167 *N*-[1-(4-chlorophenyl)-2-hydroxyethyl]-4-(cyclohexylamino)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

168 4-(cyclohexylamino)-*N*-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

169 4-(cyclohexylamino)-1-ethyl-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

170 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*S*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

171 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*R*)-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

172 4-[(1-acetyl-4-piperidinyl)amino]-*N*-(diphenylmethyl)-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

173 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-{1-[4-(methylsulfonyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

174 4-[(1-acetyl-4-piperidinyl)amino]-1-ethyl-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

175 *N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

176 *N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

177 1-ethyl-*N*-[(1*S*)-1-(4-nitrophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

178 1-ethyl-*N*-[(1*R*)-1-(4-nitrophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

179 1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

180 1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

181 1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

182 1-ethyl-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

183 1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-(1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

184 (2*R*)-[({1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl}carbonyl)amino][3-(methyloxy)phenyl]ethanoic acid

185 1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

186 1-ethyl-*N*-[1-(2-methylphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

187 *N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

188 1-ethyl-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

189 1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

190 *N*-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

191 1-ethyl-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

192 1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

193 *N*-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

194 1-ethyl-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

195 *N*-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

196 *N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

197 1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

198 1-ethyl-*N*-[1-(2-methylphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

199 1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

200 *N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

201 1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

202 *N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

203 1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

204 1-ethyl-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

205 *N*-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

206 *N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

207 *N*-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-

1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

208 *N*-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

209 *N*-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

210 *N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

211 *N*-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

212 *N*-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

213 1-ethyl-*N*-[1-(3-hydroxyphenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

214 1-ethyl-*N*-[1-(3-hydroxyphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

215 *N*-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

216 1-ethyl-*N*-{1-[3-(methyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

217 1-ethyl-*N*-{1-[4-(methyloxy)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

218 *N*-[1-(4-bromophenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

219 1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

220 *N*-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

221 1-ethyl-*N*-[1-(4-methylphenyl)propyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

222 1-ethyl-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

223 1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

224 1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

225 *N*-[1-(4-bromophenyl)-2,2,2-trifluoroethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

226 1-ethyl-4-[(4-oxocyclohexyl)amino]-*N*-{2,2,2-trifluoro-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

227 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

228 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*S*)-2-hydroxy-1-

phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

229 *N*-[1-(2,3-dihydro-1*H*-inden-5-yl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

230 *N*-[1-(4-chlorophenyl)-2-hydroxyethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

231 1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

232 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(propyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

233 1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

234 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

235 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-phenylpropyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

236 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(1-methylethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

237 *N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

238 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{(1*R*)-1-[4-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

239 1-ethyl-*N*-[1-(4-fluorophenyl)propyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

240 *N*-[1-(2,3-dichlorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

241 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

242 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-phenylethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

243 *N*-[(1*R*)-1-(4-bromophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

244 *N*-[1-(2,3-dichlorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

245 *N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

246 *N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

247 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[3-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

248 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(methyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

249 *N*-[1-(4-bromophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

250 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(propyloxy)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

251 *N*-[1-(3,5-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

252 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(4-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

253 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(1-methylethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

254 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(2-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

255 *N*-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

256 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

257 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(2-methylphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

258 1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]propyl}-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

259 *N*-(1-{4-[(difluoromethyl)oxy]phenyl}propyl)-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

260 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{1-[4-(trifluoromethyl)phenyl]propyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

261 *N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-

carboxamide

262 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[(1*R*)-1-phenylpropyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

263 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-{(1*R*)-1-[3-(methyloxy)phenyl]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

264 *N*-[1-(2,3-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

265 *N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

266 *N*-[1-(4-chloro-2-fluorophenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

267 *N*-[1-(3-chloro-4-methylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

268 *N*-[1-(2,3-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

269 *N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

270 *N*-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

271 *N*-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

272 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(3-hydroxyphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

273 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-[1-(3-hydroxyphenyl)propyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

274 *N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

275 *N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

276 *N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

277 *N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

278 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

279 1-ethyl-4-{[4-(hydroxyimino)cyclohexyl]amino}-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

280 1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

281 1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-{[4-(hydroxyimino)cyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

282 *N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

283 1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

284 *N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Isomer 1)

285 *N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Isomer 2)

286 *N*-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

287 *N*-[1-(4-chlorophenyl)propyl]-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

288 *N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-6-methyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide

289 *N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

290 *N*-[1-(4-chlorophenyl)ethyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

291 *N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

292 *N*-[1-(4-chlorophenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

293 1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

294 1-ethyl-*N*-{1-[4-(ethyloxy)phenyl]ethyl}-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

295 *N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-

pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

296 *N*-[1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

297 *N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

298 *N*-[1-(3,5-dimethylphenyl)ethyl]-1-ethyl-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

299 1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

300 1-ethyl-*N*-(1-{4-[(1-methylethyl)oxy]phenyl}ethyl)-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

301 1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

302 1-ethyl-*N*-[1-(4-fluorophenyl)ethyl]-4-[(4-oxocyclohexyl)amino]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

303 *N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 1)

304 *N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2)

305 1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Diastereoisomer 1)

306 1-ethyl-4-{[(1*S*,3*R*)- and/or (1R,3S)-3-hydroxycyclohexyl]amino}-*N*-[(1*R*)-1-(4-methylphenyl)ethyl]-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Diastereoisomer 2)

307 *N*-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2*H*-pyran-4-ylamino)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (Enantiomer 2) hydrochloride

308 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

309 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

310 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

311 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

312 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(3-chloro-4-methylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

313 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

314	4-{[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
314A	4-{*cis*-[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
315	N-[(1S)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
316	N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
317	N-[(1R)-1-(2,5-dimethylphenyl)ethyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
318	1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-N-[(1R)-1-(2,4,6-trimethylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
319	1-ethyl-N-[(1R)-1-(2-ethylphenyl)ethyl]-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
320	1-ethyl-N-[(1R)-1-(4-ethylphenyl)ethyl]-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
321	1-ethyl-N-[(1R)-1-(4-methylphenyl)propyl]-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
322	1-ethyl-N-[(1R)-1-(4-ethylphenyl)propyl]-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
323	1-ethyl-N-{(1R)-1-[4-(1-methylethyl)phenyl]propyl}-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
324	N-[(1R)-1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
325	N-[(1R)-1-(2,6-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
326	N-[(1R)-1-(2,5-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
327	1-ethyl-N-[(1R)-1-(2-ethylphenyl)propyl]-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
328	1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-N-[(1R)-1-(2,4,6-trimethylphenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
329	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(2,5-dimethylphenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
330	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-ethylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
331	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(2-ethylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
332	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(2,4,6-trimethylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
333	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

334 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(4-chlorophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

335 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-phenylpropyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

336 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[1-(4-chlorophenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

337 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[1-(4-fluorophenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

338 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

339 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-ethylphenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

340 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-{(1R)-1-[4-(1-methylethyl)phenyl]propyl}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

341 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(4-chloro-2-fluorophenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

342 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(2,6-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

343 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(2,5-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

344 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(2-ethylphenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

345 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(2,4,6-trimethylphenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

346 4-{[4-(aminocarbonyl)cyclohexyl]amino}-N-[1-(4-chlorophenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

347 4-{[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylpropyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

348 4-{[4-(aminocarbonyl)cyclohexyl]amino}-N-(1-{4-[(difluoromethyl)oxy]phenyl}ethyl)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

349 4-{[4-(aminocarbonyl)cyclohexyl]amino}-N-[1-(4-chlorophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

350 4-{[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[1-(4-fluorophenyl)propyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

351 4-{[4-(aminocarbonyl)cyclohexyl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

352 4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

353 4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

354 4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

355 4-{[*cis*-4-(aminocarbonyl)cyclohexyl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

356 4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

357 4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

358 4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

359 4-{[*trans*-4-(aminocarbonyl)cyclohexyl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

360 4-{[(3S)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

361 4-{[(3S)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

362 4-{[(3S)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

363 4-{[(3S)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

364 4-{[(3R)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

365 4-{[(3R)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

366 4-{[(3R)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

367 4-{[(3R)-1-(aminocarbonyl)pyrrolidin-3-yl]amino}-N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

368 4-{[*cis*-3-(aminocarbonyl)cyclobutyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

369 4-{[*cis*-3-(aminocarbonyl)cyclobutyl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

370 4-[(*trans*-4-acetylcyclohexyl)amino]-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

371 4-[(4-acetylcyclohexyl)amino]-N-[(1R)-1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

372 4-[(*cis*-4-acetylcyclohexyl)amino]-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

373 4-{[*cis*-4-(1-hydroxyethyl)cyclohexyl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

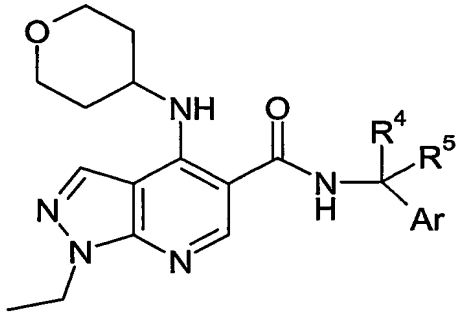
374 1-ethyl-4-{[*trans*-3-hydroxycyclohexyl]amino}-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

375 N-[(1S)-1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[*trans*-3-hydroxycyclohexyl]amino}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

376 N-[(1R)-1-(2,4-dimethylphenyl)ethyl]-1-ethyl-4-{[*trans*-3-

	hydroxycyclohexyl]amino}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
377	N-[(1R)-1-(4-bromophenyl)ethyl]-1-ethyl-4-{[*trans*-3-hydroxycyclohexyl]amino}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
378	N-[1-(3,4-dimethylphenyl)propyl]-1-ethyl-4-{[*trans*-3-hydroxycyclohexyl]amino}-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
379	N-[4-(dimethylamino)-1-(3-methylphenyl)-4-oxobutyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
380	4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[4-(dimethylamino)-1-(3-methylphenyl)-4-oxobutyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
381	1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-4-(4-piperidinylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide hydrochloride
382	N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(4-piperidinylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide hydrochloride

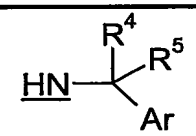
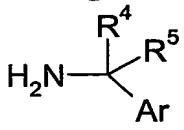
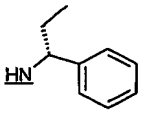
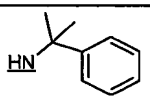
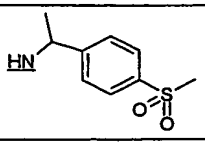
Examples 1 to 105

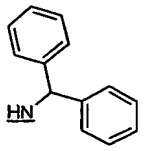
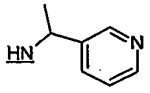
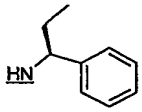
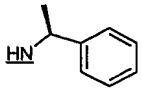
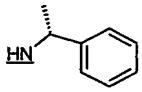
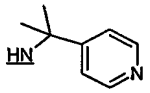
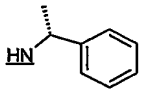
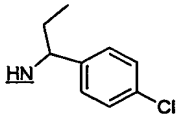
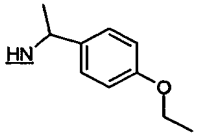
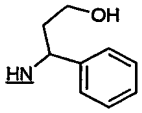
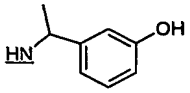
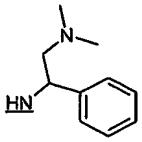
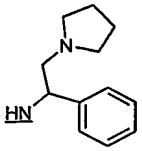


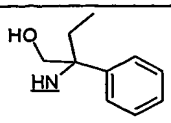
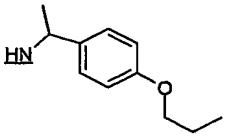
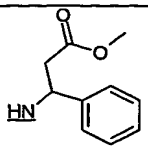
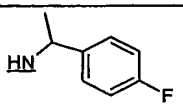
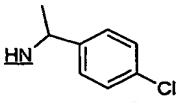
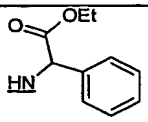
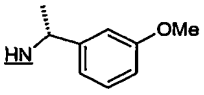
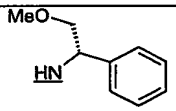
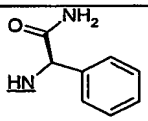
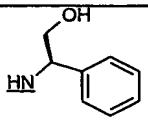
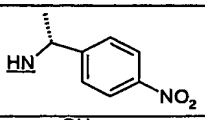
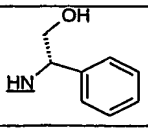
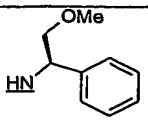
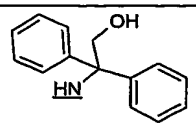
General Procedure:

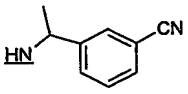
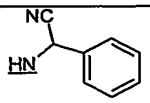
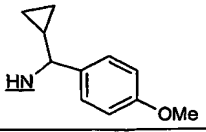
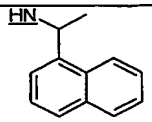
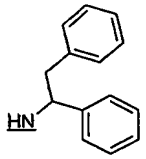
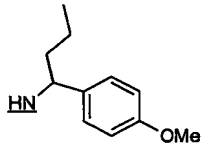
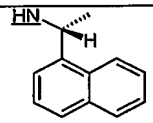
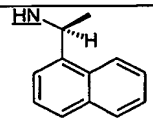
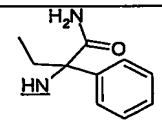
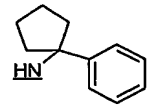
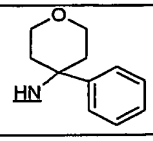
A mixture of Intermediate 13 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

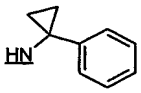
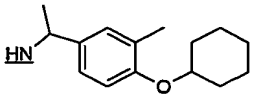
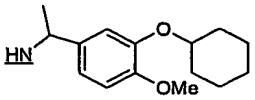
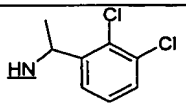
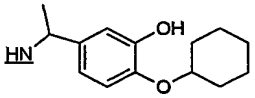
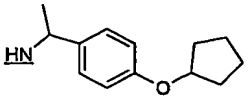
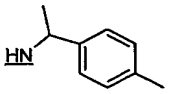
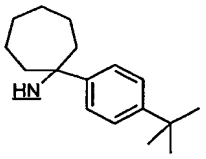
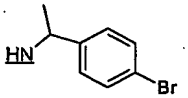
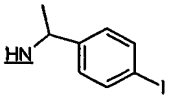
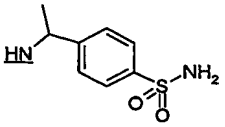
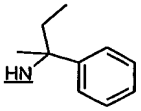
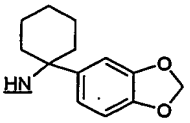
The following Examples 1 to 105 were prepared from Intermediate 13 and the appropriate amine reagent Ar-C(R^4)(R^5)-NH_2 using the above or a similar procedure:

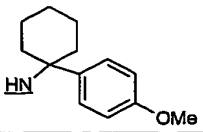
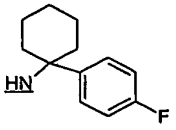
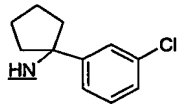
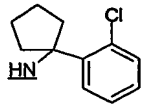
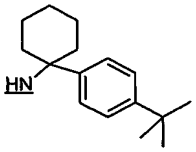
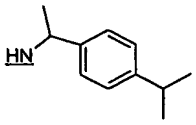
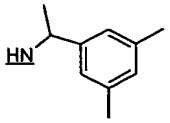
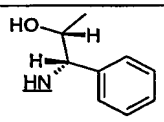
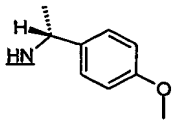
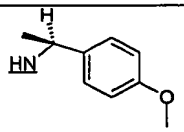
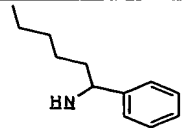
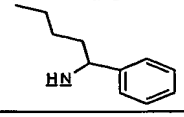
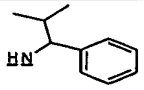
Example Number	 (connecting nitrogen underlined)	**One Possible Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
1		Lancaster	408	3.05
2		Fluorochem. Ltd.	408	2.69
3		Peakdale Molecular Ltd.	472	2.44

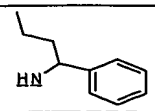
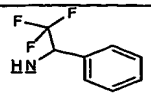
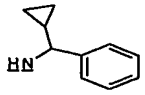
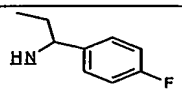
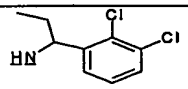
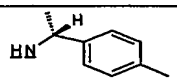
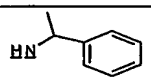
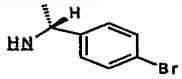
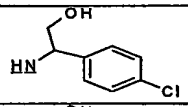
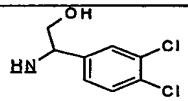
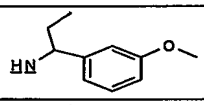
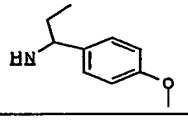
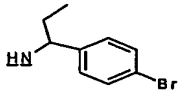
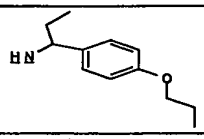
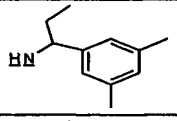
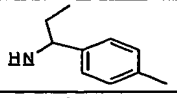
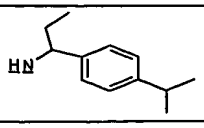
4		Aldrich	456	3.06
5			395	1.83
6		Lancaster	408	2.81
7		Aldrich	394	2.64
8		Aldrich	394	2.89
9			409	1.89
10		Aldrich	394	2.91
11		J. Pharm. Pharmacol; 1997, 49 (1), 10-15	442 + 444	3.22
12		Tim Tec Building Blocks Inc. (Intermediate 64)	438	2.98
13		Acros	424	2.71
14		Tetrahedron, 1977, 33 (5), 489-495 (Intermediate 88)	410	2.70
15		MicroChemistry Building Blocks	437	2.34
16		MicroChemistry Building Blocks	463	2.37

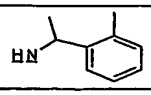
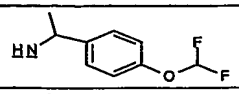
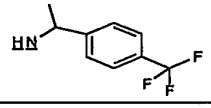
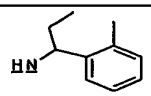
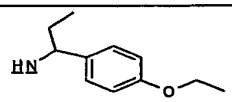
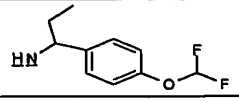
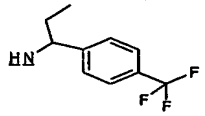
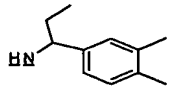
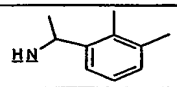
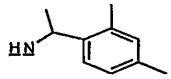
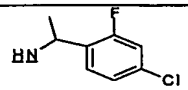
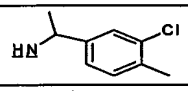
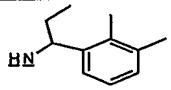
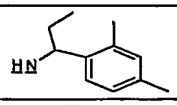
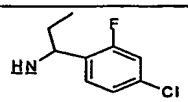
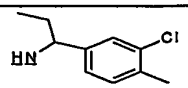
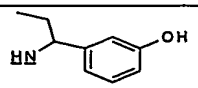
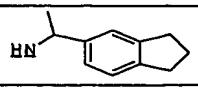
17		EP 534553 A1 (1993)	438	2.83
18		Biochem. Pharm. 1959, 2, 264-9 (no ref. To preparation)	452	3.22
19		Chembridge Europe	452	2.95
20		Aldrich	412	3.06
21		Bionet Research	428 + 430	3.24
22		Maybridge Combichem.	452	3.10
23		Lancaster	424	3.01
24		OmegaChem	424	2.90
25		Acros	423	2.57
26		Aldrich	410	2.67
27		Aldrich (hydrochloride)	439	3.07
28		Aldrich	410	2.67
29		Omega Chem	424	2.90
30		Org. Lett; 2001, 3 (2), 299-302	486	3.09

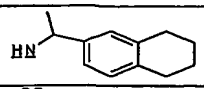
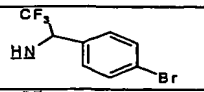
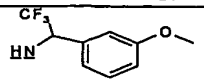
31		J. Amer. Chem. Soc; 1990, 112, 5741-5747	419	2.98
32		Aldrich	405	3.06
33		Interchim Intermediates	450	3.15
34		Fluka	444	3.36
35		Aldrich	470	3.40
36		Gaodeng Xuexiao Huaxue Xuebao, 2001, 22 (10, Suppl.), 89-91	452	3.29
37		Fluka	444	3.36
38		Fluka	444	3.36
39		Tim Tec Stock Library	451	2.36
40		Synthesis, 1978, 1, 24-6.	434	2.80
41		J. Med. Chem; 1967, 10 (1), 128-9	450	2.44

42		Org. Lett; 2003, 5 (5), 753-755	406	2.99
43		Biochem. Pharmacol., 1959, 2, 264-9 (Prep. Not given)	506	3.75
44		Not known	522	3.32
45		Sigma	462 + 464	3.38
46			508	3.28
47			478	3.39
48		Aldrich	408	3.09
49			518	3.88
50		Aldrich	472 + 474	3.22
51			520	3.30
52			473	2.57
53		SALOR	422	3.12
54			491	3.26

55			478	3.30
56			466	3.31
57			468 + 470	3.38
58			468 + 470	3.22
59			504	3.74
60		Tim Tec Building Blocks B (Intermediate 90)	436	3.36
61		Intermediate 87	422	3.23
62			424	2.58
63		Lancaster	424	2.87
64		Lancaster	424	2.98
65		Intermediate 95	450	3.54
66		Intermediate 96	436	3.39
67		Intermediate 98	422	3.19

68		Intermediate 99	422	3.17
69		Intermediate 92	448	3.21
70		Intermediate 97	420	3.09
71		US 4154599 (1980)	426	3.18
72			476	3.53
73		Lancaster	408	3.14
74		Aldrich	394	2.99
75		Lancaster	472	3.28
76		Ger. Offen DE4443892 (1996)	445	2.85
77		WO 9709335 (1997)	478	2.95
78		Intermediate 72	438	3.12
79		Intermediate 73	438	3.10
80		Intermediate 74	486	3.39
81		Intermediate 77	466	3.41
82		Intermediate 85	436	3.39
83		Intermediate 75	422	3.26
84		Intermediate 80	450	3.51

85		Intermediate 63	408	3.13
86		Intermediate 65	460	3.17
87		Intermediate 66	462	3.67
88		Intermediate 70	422	3.40
89		Intermediate 76	452	3.24
90		Intermediate 78	474	3.28
91		Intermediate 79	476	3.81
92		Intermediate 84	436	3.37
93		Intermediate 67	422	3.46
94		Intermediate 62	422	3.28
95		Intermediate 68	446	3.31
96		Intermediate 69	442	3.36
97		Intermediate 81	436	3.58
98		Intermediate 82	436	3.41
99		Intermediate 83	460	3.43
100		Intermediate 86	456	4.02
101		Intermediate 71	424	2.87
102		Intermediate 90	433	3.18

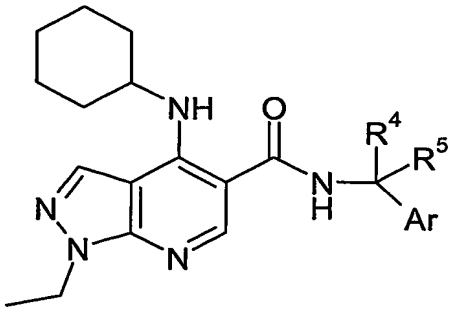
103		Intermediate 91	447	3.29
104		Intermediate 93	527	3.35
105		Intermediate 94	478	3.14

When Examples 78 to 101 are made from an amine reagent Ar-C(R^4)(R^5)-NH_2 which is an appropriate one of Intermediates 62 to 86 (excluding Intermediates 75a, 80a, 82a, 82b, and 83a) as disclosed in the Examples 1-105 table above, then Examples 78 to 101 are believed to be a mixture of enantiomers with the major enantiomer believed to have the (R)-stereochemistry (i.e. at the benzylic carbon atom).

Alternative Preparation of Example 73

A solution of Intermediate 13 (2.0g) in thionyl chloride (20ml) was stirred and heated at reflux for 2.5 hours. The solution was cooled and the thionyl chloride was removed *in vacuo* to leave the intermediate acid chloride (2.1g). A solution of the acid chloride (2.1g), (R)-1-(4-methylphenyl)ethylamine (1.0g) and DIPEA (1.4g) in THF (100ml) was stirred for 18 hours. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between 0.5M sodium bicarbonate (250ml) and ethyl acetate (250ml). The organic phase was separated, washed with water (250ml), dried over Na_2SO_4 and concentrated *in vacuo* to give a foam. The foam was crystallised from a (5:1) mixture of cyclohexane and Et_2O. One recrystallisation from a (5:1) mixture of cyclohexane and Et_2O gave Example 73 (0.96g) as white needles.
LC-MS showed $MH^+ = 408$; $T_{RET} = 3.05$ min.

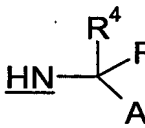
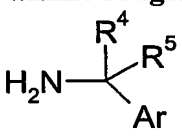
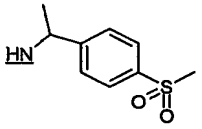
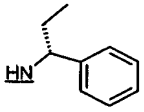
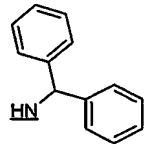
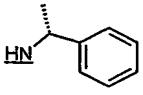
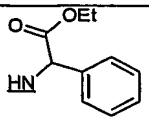
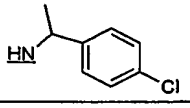
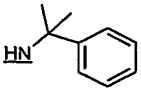
Examples 106 to 169

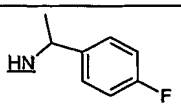
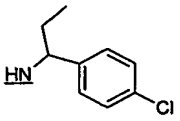
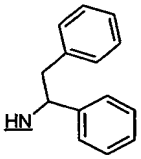
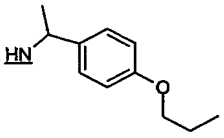
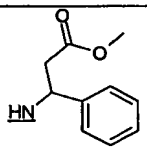
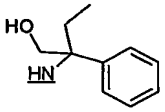
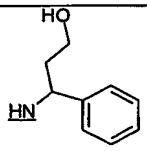
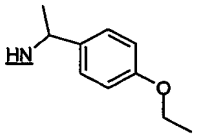
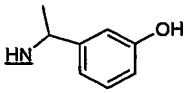
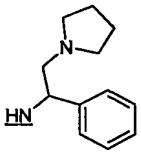
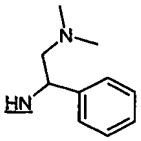
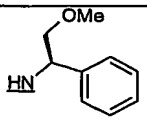


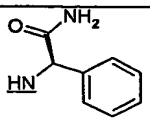
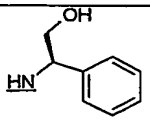
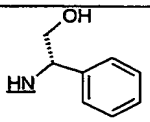
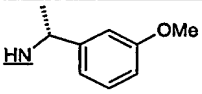
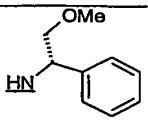
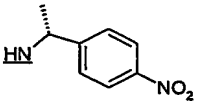
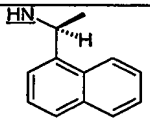
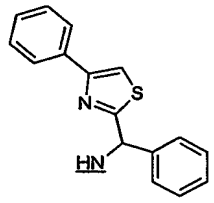
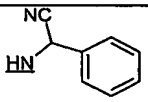
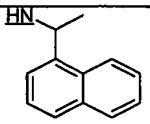
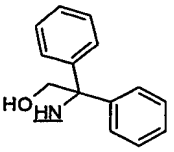
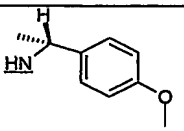
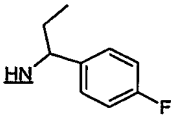
General Procedure:

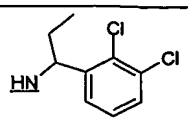
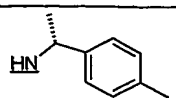
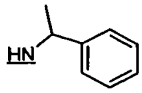
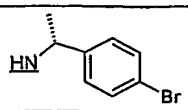
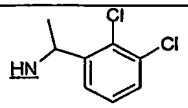
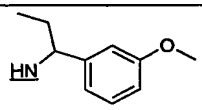
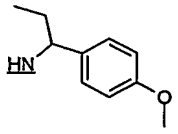
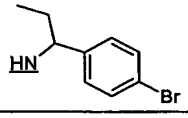
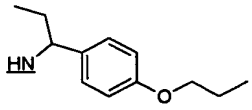
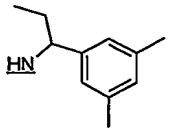
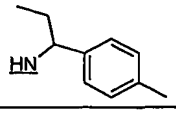
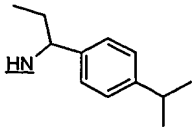
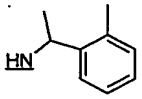
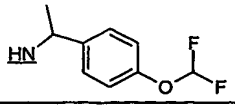
A mixture of Intermediate 14 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

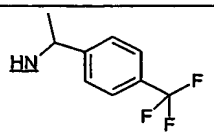
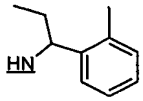
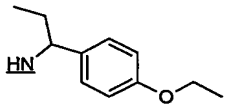
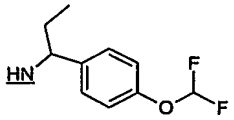
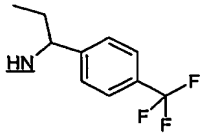
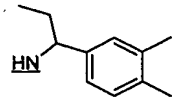
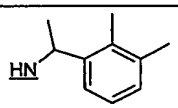
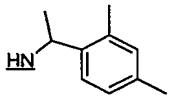
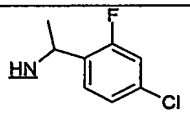
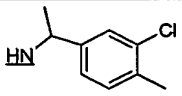
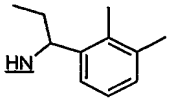
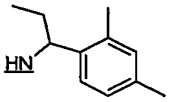
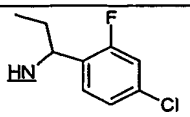
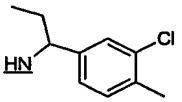
The following Examples 106 to 169 were prepared from Intermediate 14 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using the above or a similar procedure:

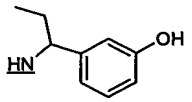
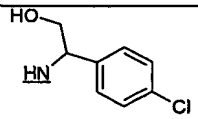
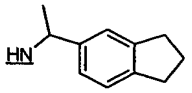
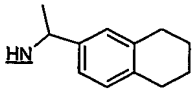
Example Number	 (connecting nitrogen underlined)	One Possible Source of amine reagent 	MH^+ Ion	LC-MS retention time
106		Peakdale Molecular Ltd.	470	3.25
107		Lancaster	406	3.72
108		Aldrich	454	3.88
109		Aldrich	392	3.60
110		Maybridge Combichem	450	3.65
111		Bionet Research	426	3.82
112		Fluorochem. Ltd.	406	3.64

113		Aldrich	410	3.64
114			440	3.93
115		Aldrich	468	3.90
116			450	3.78
117		Chembridge Europe	450	3.49
118			436	3.39
119		Acros	422	2.81
120		Tim Tec Building Blocks Inc. (Intermediate 64)	436	3.22
121		Intermediate 88	408	2.87
122		MicroChemistry Building Blocks	461	2.26
123		MicroChemistry Building Blocks	436	2.23
124		Omega Chem	422	3.47

125			421	3.08
126		Aldrich	408	3.21
127		Aldrich	408	3.21
128		Lancaster	422	4.97
129		Omega Chem	422	3.02
130		Aldrich (hydrochloride)	437	3.20
131		Fluka	442	3.45
132			537	4.01
133		Aldrich (hydrochloride)	403	3.60
134		Fluka	442	3.90
135			484	3.57
136		Lancaster	422	3.54
137		US 4154599 (1980)	424	3.75

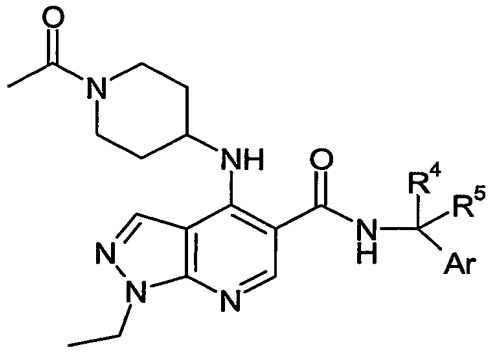
138			474	4.13
139		Lancaster	406	3.71
140		Aldrich	392	3.58
141		Lancaster	470	3.85
142		Sigma	460	4.03
143		Intermediate 72	436	3.68
144		Intermediate 73	436	3.65
145		Intermediate 74	484	3.97
146		Intermediate 77	464	3.94
147		Intermediate 85	434	3.95
148		Intermediate 75	420	3.83
149		Intermediate 80	448	4.05
150		Intermediate 63	406	3.74
151		Intermediate 65	458	3.84

152		Intermediate 66	460	3.84
153		Intermediate 70	420	3.87
154		Intermediate 76	450	4.34
155		Intermediate 78	472	4.00
156		Intermediate 79	474	3.95
157		Intermediate 84	434	3.93
158		Intermediate 67	420	3.85
159		Intermediate 62	420	3.86
160		Intermediate 68	444	4.39
161		Intermediate 69	440	4.10
162		Intermediate 81	434	3.96
163		Intermediate 82	434	3.99
164		Intermediate 83	458	4.37
165		Intermediate 86	454	4.26

166		Intermediate 71	422	3.43
167		Ger. Offen DE4443892 (1996)	442	3.38
168		Intermediate 90	431	3.76
169		Intermediate 91	445	3.96

When Examples 143 to 166 are made from an amine reagent Ar-C(R^4)(R^5)-NH_2 which is an appropriate one of Intermediates 62 to 86 (excluding Intermediates 75a, 80a, 82a, 82b, and 83a) as disclosed in the Examples 106-169 table above, then Examples 143 to 166 are believed to be a mixture of enantiomers with the major enantiomer believed to have the (R)-stereochemistry (i.e. at the benzylic carbon atom).

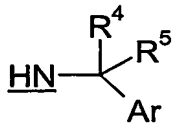
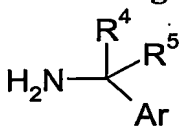
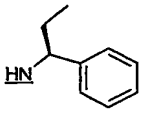
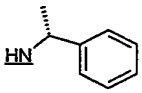
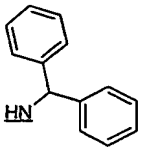
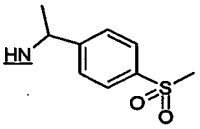
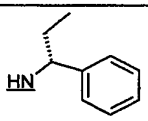
Examples 170 to 174



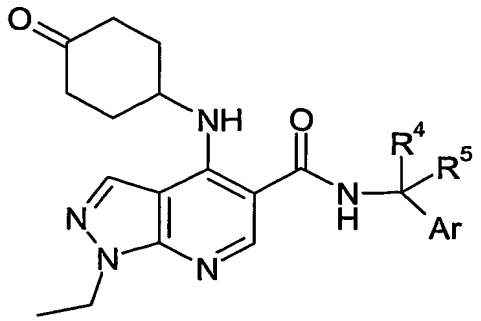
General Procedure:

A mixture of Intermediate 15 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

The following Examples 170 to 174 were prepared from Intermediate 15 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using the above or a similar procedure:

Example Number	 (connecting nitrogen underlined)	One Possible Source of amine reagent 	MH^+ Ion	LC-MS retention time
170		Lancaster	449	2.94
171		Aldrich	435	2.84
172		Aldrich	497	3.16
173		Peakdale Molecular Ltd.	513	2.63
174		Lancaster	449	2.95

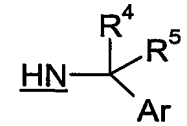
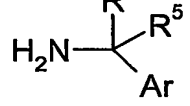
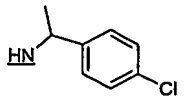
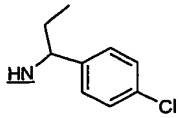
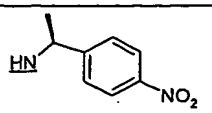
Examples 175 to 226

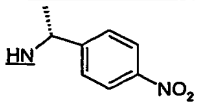
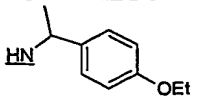
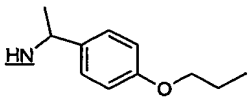
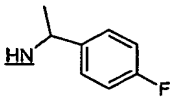
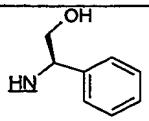
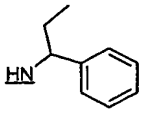
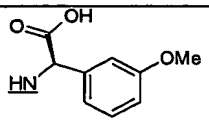
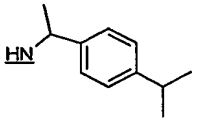
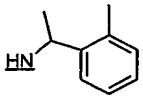
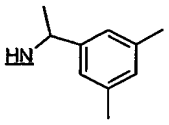
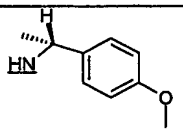
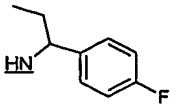
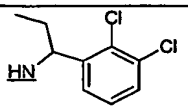
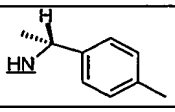


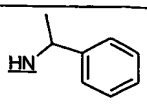
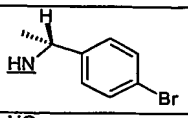
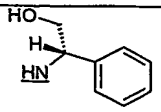
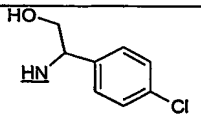
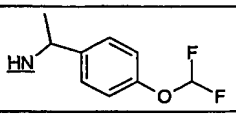
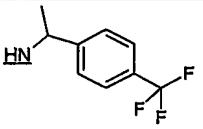
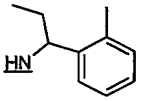
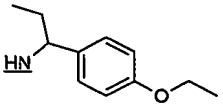
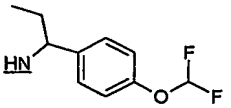
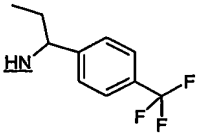
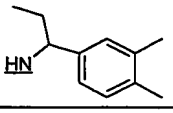
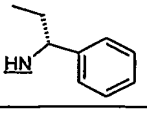
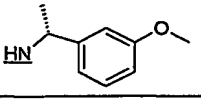
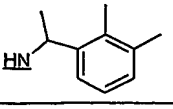
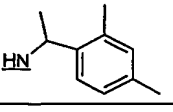
General Procedure:

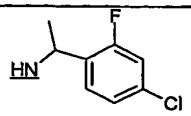
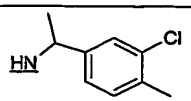
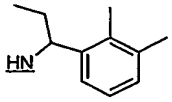
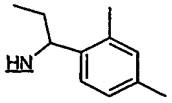
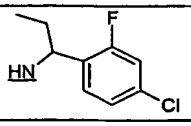
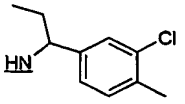
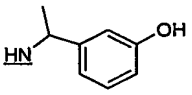
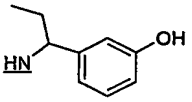
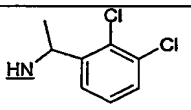
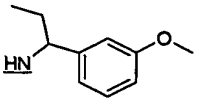
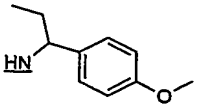
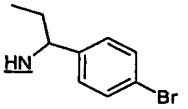
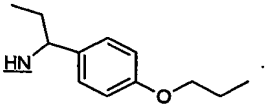
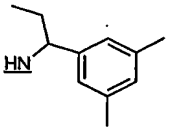
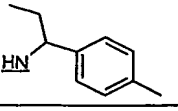
A mixture of Intermediate 16 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

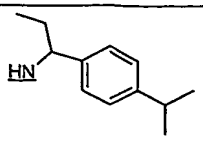
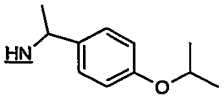
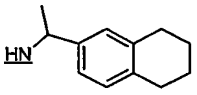
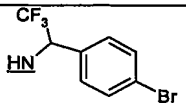
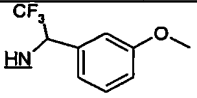
The following Examples 175 to 226 were prepared from Intermediate 16 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using the above or a similar procedure:

Example Number	 (connecting nitrogen underlined)	One Possible Source of amine reagent 	MH^+ Ion	LC-MS retention time
175		Bionet Research	440	3.22
176			454	3.20
177		Aldrich (hydrochloride)	451	3.02

178		Aldrich (hydrochloride)	451	3.02
179		Tim Tec Building Blocks Inc. Intermediate 64	450	3.06
180		GR87015X/A	464	3.26
181		Aldrich	424	3.02
182		Aldrich	422	2.64
183		Aldrich	420	3.06
184			466	2.76
185		Tim Tec Building Blocks B Intermediate 89	448	3.36
186		Tim Tec Building Blocks B	420	2.79
187		Intermediate 87	434	3.25
188		Lancaster	436	2.99
189			438	3.19
190			488	3.52
191		Lancaster	420	3.15

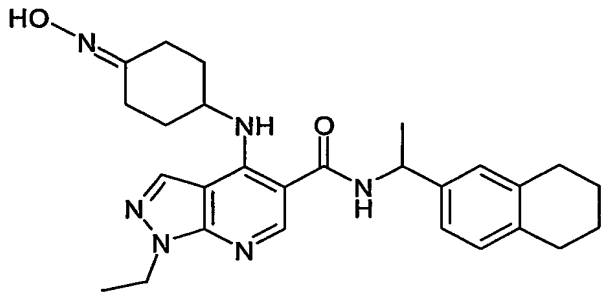
192		Aldrich	406	3.01
193		Lancaster	484	3.28
194		Aldrich	422	2.54
195		Ger. Offen DE4443892 (1996)	456	2.86
196		Intermediate 65	472	2.85
197		Intermediate 66	474	3.00
198		Intermediate 70	434	2.92
199		Intermediate 76	464	2.90
200		Intermediate 78	486	2.96
201		Intermediate 79	488	3.11
202		Intermediate 84	448	3.02
203		Lancaster	420	2.79
204		Lancaster	436	2.67
205		Intermediate 67	434	2.90
206		Intermediate 62	434	2.93

207		Intermediate 68	458	2.98
208		Intermediate 69	454	3.03
209		Intermediate 81	448	3.03
210		Intermediate 82	448	3.05
211		Intermediate 83	472	3.10
212		Intermediate 86	468	3.14
213		Intermediate 88	422	2.44
214		Intermediate 71	436	2.56
215		Sigma	474	3.41
216		Intermediate 72	450	3.13
217		Intermediate 73	450	3.12
218		Intermediate 74	498	3.39
219		Intermediate 77	478	3.42
220		Intermediate 85	448	3.39
221		Intermediate 75	434	3.48

222		Intermediate 80	462	3.54
223		J. Chem. Soc. Abstracts 1951, 3430-3	464	3.19
224		Intermediate 91	460	3.39
225		Intermediate 93	539	3.45
226		Intermediate 94	490	3.24

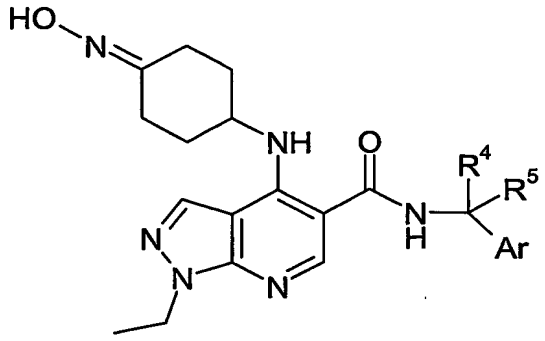
When Examples 196 to 202, 205 to 212, 214, and 216 to 222 are made from an amine reagent Ar-C(R^4)(R^5)-NH_2 which is an appropriate one of Intermediates 62 to 86 (excluding Intermediates 75a, 80a, 82a, 82b, and 83a) as disclosed in the Examples 175-226 table above, then Examples 196 to 202, 205 to 212, 214, and 216 to 222 are believed to be a mixture of enantiomers with the major enantiomer believed to have the (R)-stereochemistry (i.e. at the benzylic carbon atom).

Example 227

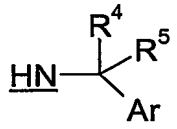
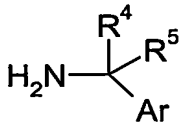
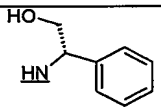
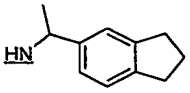
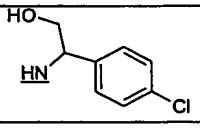


A mixture of Intermediate 17 (25mg, 0.079mmol), HATU (35mg, 0.092mmol) and DIPEA (50mg, 0.387mmol) in MeCN (2.0ml) was stirred at room temperature for 10 min. Intermediate 91 (30mg, 0.142mmol) was then added and the mixture was stirred for 2.5 hours then left to stand overnight. The solution was concentrated *in vacuo*. The residue was dissolved in EtOAc and applied to a SPE cartridge (silica, 5g). The cartridge was eluted with EtOAc. Fractions containing the desired product were concentrated *in vacuo* to give Example 227 as a white solid. LCMS showed $MH^+ = 475$; $T_{RET} = 3.32$min.

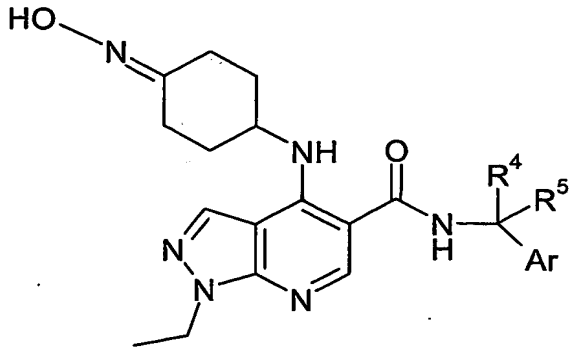
Examples 228 to 230



The following Examples 228 to 230 were prepared from Intermediate 17 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using a similar procedure to that used for the preparation of Example 227:

Example Number	 (connecting nitrogen underlined)	One Possible Source of amine reagent 	MH^+ Ion	LC-MS retention time
228		Aldrich	438	2.59
229		Intermediate 90	461	3.19
230		Ger. Offen DE4443892 (1996)	471	2.78 + 2.81

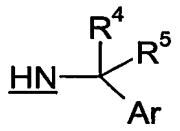
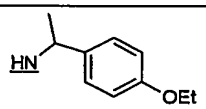
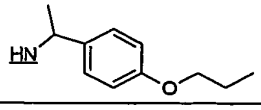
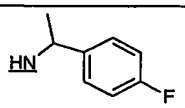
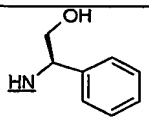
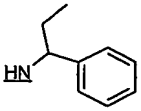
Examples 231 to 281

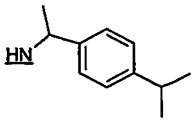
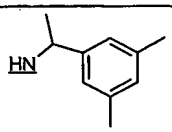
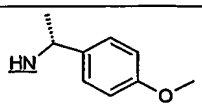
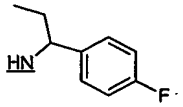
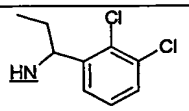
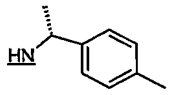
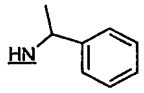
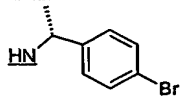
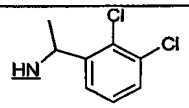
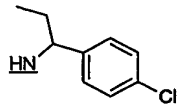
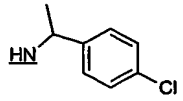
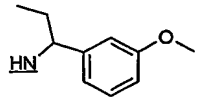
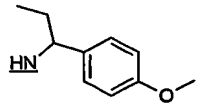
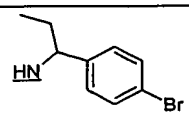
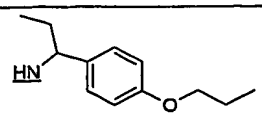


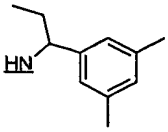
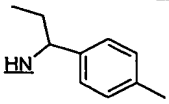
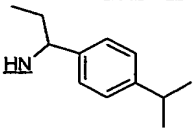
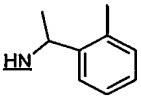
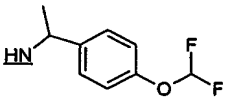
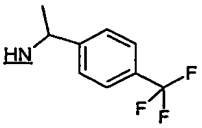
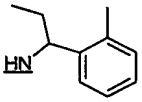
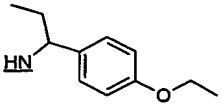
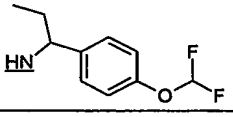
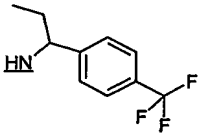
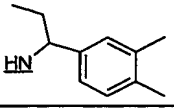
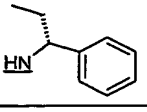
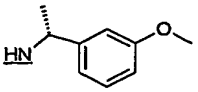
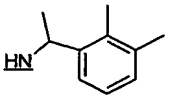
General Procedure:

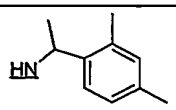
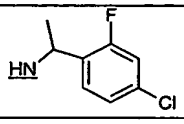
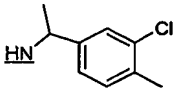
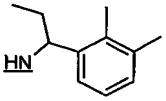
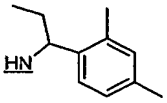
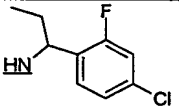
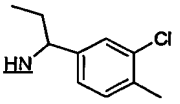
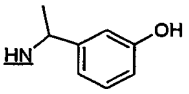
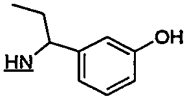
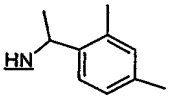
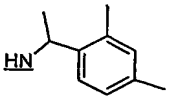
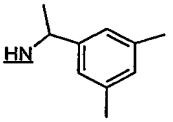
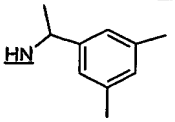
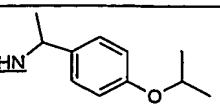
A mixture of the appropriate ketone (0.05mmol), hydroxylamine hydrochloride (0.07mmol) and DIPEA (0.05ml) in MeCN (1.0ml) was heated at reflux for 5 hours. The solvent was removed. The residue was dissolved in chloroform and applied to a SPE cartridge (silica, 0.5g). The cartridge was eluted with EtOAc. Fractions containing the desired product were concentrated *in vacuo* to give the appropriate oxime.

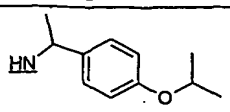
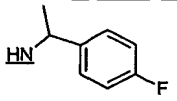
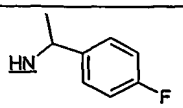
The following Examples 231 to 281 were prepared in the above or a similar manner:

Example Number	 (connecting nitrogen underlined)	Starting Ketone	MH^+ Ion	LC-MS retention time
231		Example 179	465	2.92
232		Example 180	479	3.09
233		Example 181	439	2.87
234		Example 182	437	2.47,2.51
235		Example 183	435	3.02

236		Example 185	463	3.28
237		Example 187	449	3.15
238		Example 188	451	2.58
239		Example 189	453	2.78
240		Example 190	503	3.11
241		Example 191	435	2.72
242		Example 192	421	2.58
243		Example 193	499	2.86
244		Example 215	489	3.01
245		Example 176	469	2.94
346		Example 175	455	2.82
247		Example 216	465	2.72
248		Example 217	465	2.70
249		Example 218	513	2.98
250		Example 219	493	2.99

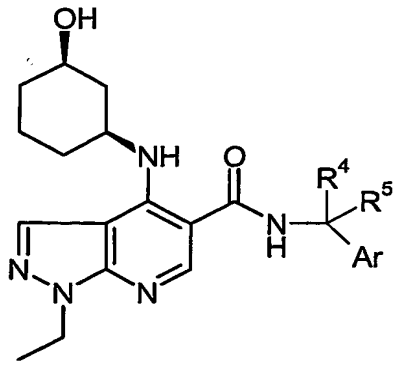
251		Example 220	463	2.96
252		Example 221	449	2.84
253		Example 222	477	3.08
254		Example 186	435	2.72
255		Example 196	487	2.77
256		Example 197	489	2.92
257		Example 198	449	2.83
258		Example 199	479	2.82
259		Example 200	501	2.88
260		Example 201	503	3.02
261		Example 202	463	2.99
262		Example 203	435	2.71
263		Example 204	451	2.60
264		Example 205	449	2.82

265		Example 206	449	2.84
266		Example 207	473	2.90
267		Example 208	469	2.94
268		Example 209	463	2.93
269		Example 210	463	2.95
270		Example 211	487	3.01
271		Example 212	483	3.05
272		Example 213	437	2.40
273		Example 214	451	2.52
274	 Isomer 1	Example 295	449	3.05
275	 Isomer 2	Example 296	449	3.05
276	 Isomer 1	Example 297	449	3.06
277	 Isomer 2	Example 298	449	3.06
278		Example 299	479	3.01

	Isomer 1			
279	 Isomer 2	Example 300	479	3.01
280	 Isomer 1	Example 301	439	2.90
281	 Isomer 2	Example 302	439	2.90

When Examples 196 to 202, 205 to 212, 214, and 216 to 222 are made from an amine reagent Ar-C(R^4)(R^5)-NH_2 which is an appropriate one of Intermediates 62 to 86 (excluding Intermediates 75a, 80a, 82a, 82b, and 83a) as disclosed in the Examples 175-226 table above, then the derived Examples 247 to 253, 255 to 261, 264 to 271, and 273 disclosed in the Examples 231-281 table above are generally believed to be a mixture of isomers with the major isomer(s) believed to have the (R)-stereochemistry (i.e. at the benzylic carbon atom).

Examples 282 to 286

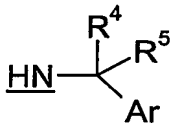
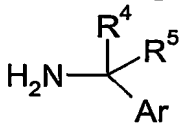
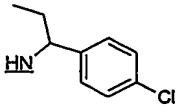
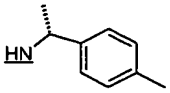
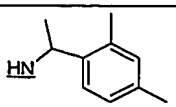


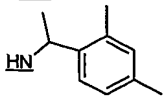
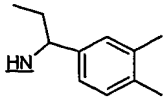
[*cis*-(3-hydroxycyclohex-1-yl)amino group; (1:1) mixture of *cis*-stereoisomers]

General Procedure:

A mixture of Intermediate 19 (0.075mmol), HATU (0.09mmol) and DIPEA (0.19mmol) in MeCN (2.0ml) was stirred at room temperature for 10min. then added to the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.075mmol). The reaction mixture was stirred at room temperature for 7h. The solvent was removed by blowing nitrogen over the reaction mixture. The residue was partitioned between EtOAc (5ml) and 0.5M sodium bicarbonate (5ml). The organic phase was separated, washed with water (5ml) and dried over $MgSO_4$. The solvent was blown off and the residue dried *in vacuo* to leave the desired product.

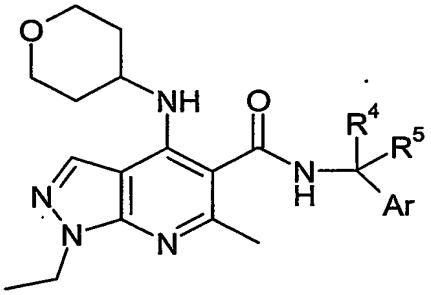
The following Examples 282-286 were prepared from Intermediate 19 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

Example Number	 (connecting nitrogen underlined)	**One Possible Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
282			456	3.19
283		Lancaster	422	2.91
284	 Isomer 1	Intermediate 100	436	3.12

285	 Isomer 2	Intermediate 101	436	3.14
286		Intermediate 84	450	3.15

When Example 286 is made from an amine reagent Ar-C(R^4)(R^5)-NH_2 which is Intermediates 84 as disclosed in the table above, then Example 286 is believed to be a mixture of isomers with the major isomer(s) believed to have the (R)-stereochemistry (i.e. at the benzylic carbon atom).

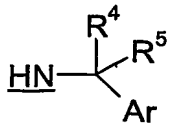
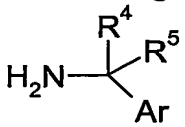
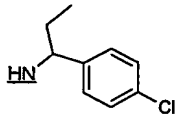
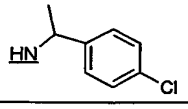
Examples 287 to 288



General Procedure:

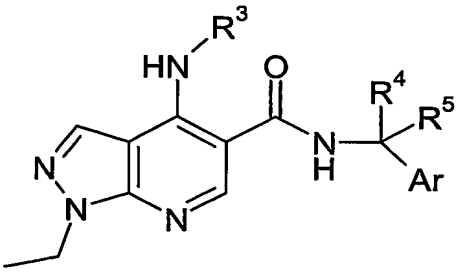
A mixture of Intermediate 18 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

The following Examples 287-288 were prepared from Intermediate 18 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

Example Number	 (connecting nitrogens underlined)	One Possible Source of amine reagent 	MH^+ Ion	LC-MS retention time
287			456 + 458	2.88
288		Bionet Research	442 + 444	2.73

Examples 289 to 306

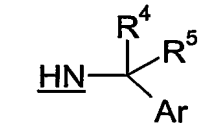
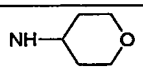
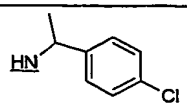
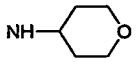
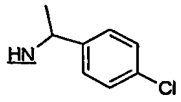
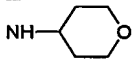
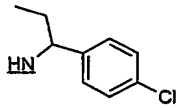
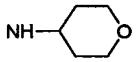
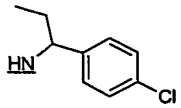
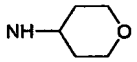
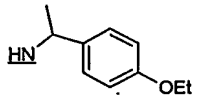
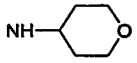
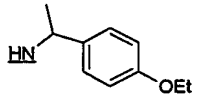
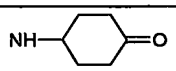
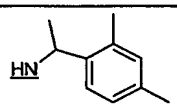
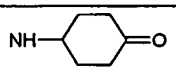
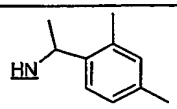
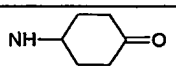
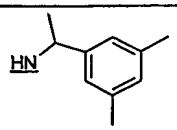
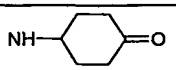
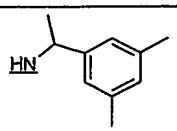
Separation of isomers of Examples on Chiral Columns

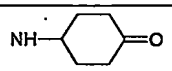
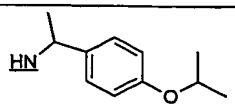
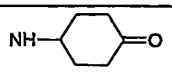
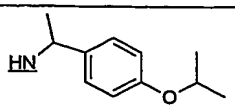
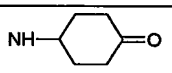
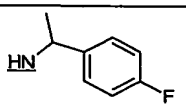
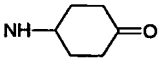
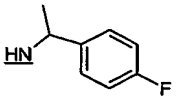
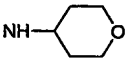
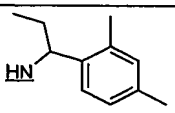
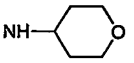
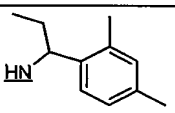
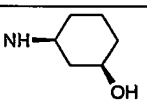
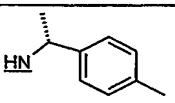
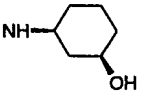
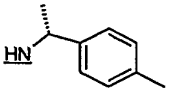


General Procedure:

The Examples below, which were generally either believed to be racemic or believed to be a mixture of isomers generally enriched in major isomer(s) believed to have the (R)-stereochemistry (i.e. at the benzylic carbon atom), were resolved by preparative chiral column chromatography, using either a 2-inch x 20cm Whelk 0-1 chiral column with 100% EtOH or a mixture of EtOH and n-heptane as the eluent or a 2-inch ChiralPak AD chiral column with 100% ethanol as the eluent. In the Table, "Isomer 1" relates to the first enantiomer to be eluted from the column and "Isomer 2" relates to the second enantiomer.

Example 283 (mixture of diastereoisomers) was also separated into its component isomers by preparative chiral column chromatography, using a 2-inch ChiralCel OD chiral column with a (95:5) mixture of heptane and ethanol as the eluent. In the Table, "Isomer 1" relates to the first enantiomer to be eluted from the column and "Isomer 2" relates to the second enantiomer.

Example Number	NHR^3		Starting Material	MH^+ Ion	LC-MS retention time
289		 Isomer 1	Example 21	428	3.18
290		 Isomer 2	Example 21	428	3.18
291		 Isomer 1	Example 11	442	3.30
292		 Isomer 2	Example 11	442	3.30
293		 Isomer 1	Example 12	438	3.07
294		 Isomer 2	Example 12	438	3.07
295		 Isomer 1	Example 206	434	3.25
296		 Isomer 2	Example 206	434	3.25
297		 Isomer 1	Example 187	434	3.25
298		 Isomer 2	Example 187	434	3.26

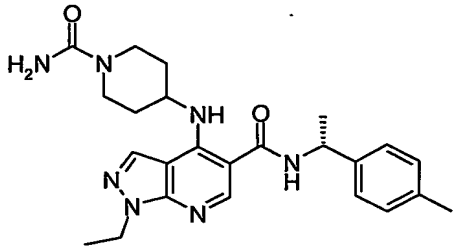
299		 Isomer 1	Example 223	464	3.21
300		 Isomer 2	Example 223	464	3.19
301		 Isomer 1	Example 181	424	2.93
302		 Isomer 2	Example 181	424	2.93
303		 Isomer 1	Example 98	436	3.36
304		 Isomer 2	Example 98	436	3.36
305	 *Cis* Isomer 1		Example 283	422	2.90
306	 *Cis* Isomer 2		Example 283	422	2.90

Example 307 Preparation of the Hydrochloride of Example 304

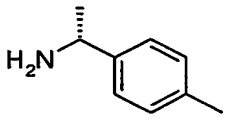
_N_-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-4-(tetrahydro-2_H_-pyran-4-ylamino)-1_H_-pyrazolo[3,4-_b_]pyridine-5-carboxamide (Enantiomer 2) hydrochloride

A solution of Example 304 (1.3g) in Et_2O (30ml) was treated, rapidly dropwise with stirring, with a molar excess (relative to Example 304, i.e. more than 1 mole equivalent cf. Example 304) of 1.0M hydrogen chloride in Et_2O. The resultant suspension was left to stand for 2 hours. The solvent was removed *in vacuo*. The residual solid was recrystallised from ethanol to give the hydrochloride (0.64g) as white needles. LC-MS showed $MH^+ = 436$; $T_{RET} = 3.35$ min.

Example 308: 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-(4-methylphenyl)ethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

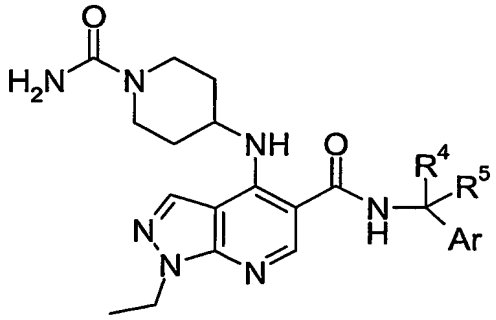


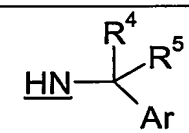
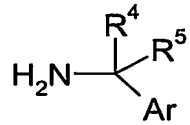
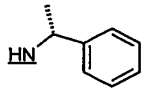
A solution of Intermediate 105 (0.066mmol) in DMF (1ml) was treated with EDC (0.066mmol), HOBT (0.066mmol) and DIPEA (0.151mmol) followed by

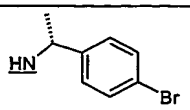
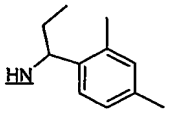
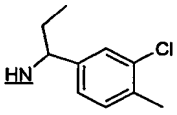
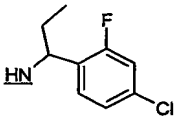


(0.066mmol) (e.g. available from Lancaster Synthesis), for example at room temperature. The reaction mixture was left to stand at 22°C for 16h. The DMF was evaporated and the residue was partitioned between DCM (5ml) and saturated aqueous sodium bicarbonate (2ml). The organic layer was collected through a hydrophobic frit and evaporated. The residue was purified by mass directed autoprep. HPLC to give the title compound as a gum (8.9mg). LCMS showed $MH^+ = 450$; $T_{RET} = 2.76$min.

The following **Examples 309 to 313** were prepared from Intermediate 105 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using substantially the above procedure:

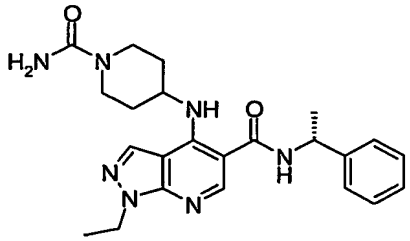


Example Number	 (connecting nitrogen underlined)	One possible Source of amine  reagent	MH^+ Ion	LC-MS retention time
309		Aldrich	436	2.62

310		Lancaster	516	2.8
311		Intermediate 82	478	2.96
312		Intermediate 86	498	2.9
313		Intermediate 83	502	2.88

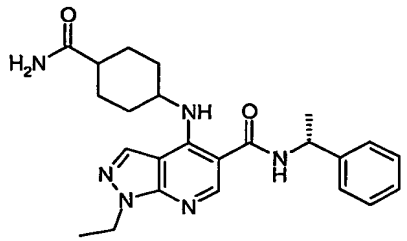
When Examples 311, 312 and 313 are made from Intermediates 82, 86 and 83 respectively, as disclosed in the table above, then Examples 311, 312 and 313 are believed to be a mixture of enantiomers with the major enantiomer believed to have the (R)-stereochemistry (i.e. at the benzylic carbon atom).

Alternative Preparation of Example 309: 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



A mixture of Intermediate 109 (27mg) and Intermediate 111 (16mg) in MeCN (2ml) was treated with DIPEA (35μL). The reaction mixture was heated under reflux for 72h. The solvent was evaporated and the residue was partitioned between DCM (5ml) and saturated aqueous sodium bicarbonate (2ml). The organic layer was collected through a hydrophobic frit and evaporated. The residue was purified by mass directed autoprep. HPLC to give Example 309 as a white solid (5.0mg). LCMS showed $MH^+ = 436$; $T_{RET} = 2.62$min.

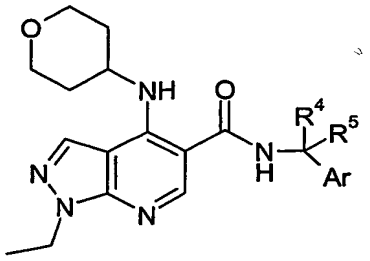
Example 314: 4-{[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



A solution of Intermediate 109 (0.08mmol) in MeCN (1ml) was treated with Intermediate 113 (0.088mmol) and DIPEA (0.2mmol). The reaction mixture was heated at reflux for 20h. The solvents were evaporated and the residue was partitioned between DCM (5ml) and water (2ml). The organic phase was collected through a hydrophobic frit and evaporated. The residue was purified by mass directed autoprep. HPLC to give **Example 314** as a white solid (12.2mg). LCMS showed $MH^+ = 435$; $T_{RET} = 2.7$min.

In Example 314, the R^3NH group, i.e. the [4-(aminocarbonyl)cyclohexyl]amino group, is preferably in the *cis* configuration. In this case, **(Example 314A)**, it is 4-{*cis*-[4-(aminocarbonyl)cyclohexyl]amino}-1-ethyl-N-[(1R)-1-phenylethyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide.

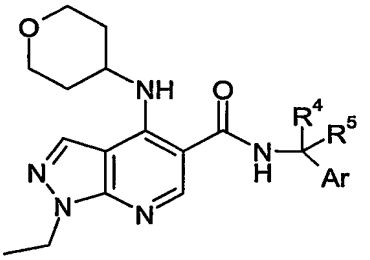
Examples 315 to 328



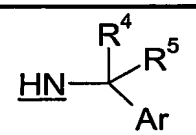
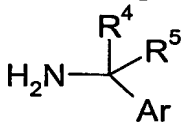
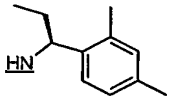
General Procedure:

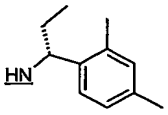
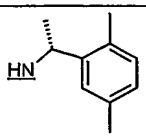
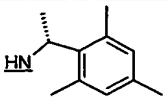
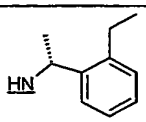
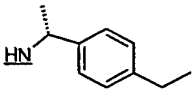
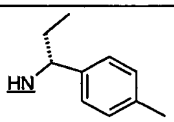
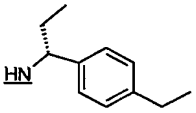
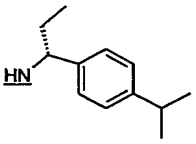
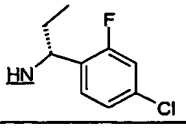
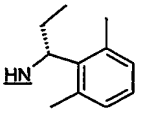
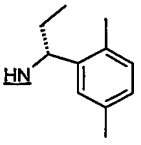
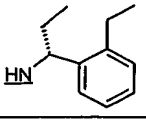
A mixture of Intermediate 13 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

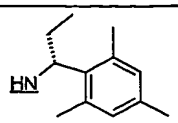
The following Examples 315 to 328 were prepared from Intermediate 13 and the appropriate amine reagent Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:



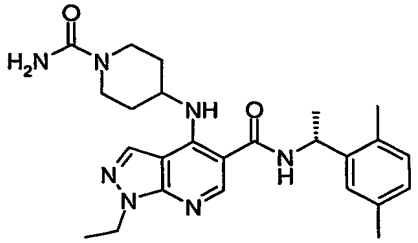
(of which, Examples 316 to 328 are believed to consist essentially of an enantiomer having the (R)-stereochemistry at the benzylic carbon atom, as shown below)

Example Number	 (connecting nitrogen underlined)	Preferred Source of amine reagent 	MH^+ Ion	LC-MS retention time
315	 (essentially one	Intermediate 82a	436	3.31

	enantiomer)			
316	 (essentially one enantiomer)	Intermediate 82b	436	3.31
317		Intermediate 139	422	3.21
318		Intermediate 140	436	3.34
319		Intermediate 137	422	3.23
320		Intermediate 138	422	3.23
321		Intermediate 75a	422	3.04
322		Intermediate 142	436	3.19
323		Intermediate 80a	450	3.32
324		Intermediate 83a	460	3.24
325		Intermediate 144	436	3.17
326		Intermediate 143	436	3.19
327		Intermediate 141	436	3.19

328		Intermediate 145	450	3.31

Example 329: 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[(1R)-1-(2,5-dimethylphenyl)ethyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

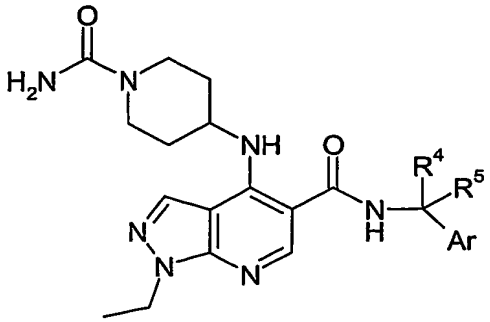


(believed to consist essentially of an enantiomer believed to have the (R)-stereochemistry at the benzylic carbon atom, as shown above)

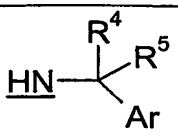
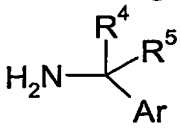
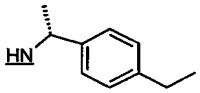
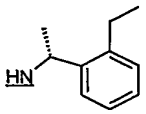
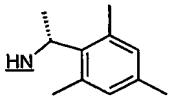
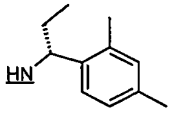
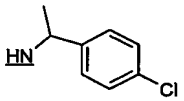
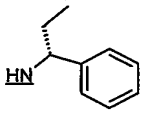
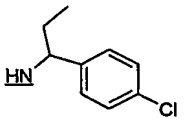
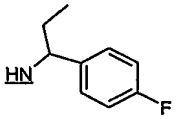
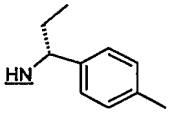
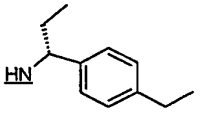
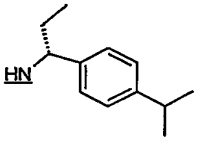
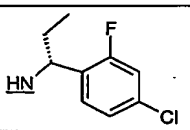
A solution of Intermediate 105 (29mg), HATU (36mg) and DIPEA (0.037ml) in acetonitrile (5ml) was stirred at room temperature for 10min. Intermediate 139 (18mg) was added. The reaction mixture was left to stand at 22°C for 16h. The solvent was evaporated. The residue was dissolved in chloroform and applied to an SPE cartridge (aminopropyl, 2g). The cartridge was eluted initially with chloroform and then with 20% methanol in ethyl acetate, to give Example 329 (23mg) as an amorphous solid. LCMS showed $MH^+ = 464$; $T_{RET} = 2.87$min.

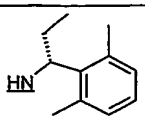
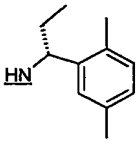
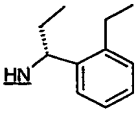
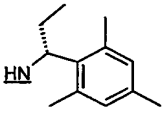
Examples 330 to 345

The following Examples 330 to 345 were prepared from Intermediate 105 and the appropriate amine Ar-C(R^4)(R^5)-NH_2 using the same or a similar procedure to that used for Example 329 e.g. with the same or similar numbers of moles of reagents:

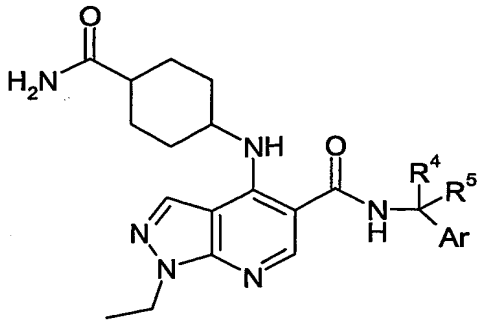


(of which, Examples 330 to 333, Example 335 and Examples 338 to 345, are believed to consist essentially of an enantiomer believed to have the (R)-stereochemistry at the benzylic carbon atom, as shown below)

Example Number	 (connecting nitrogen underlined)	One Possible Source of amine reagent 	MH^+ Ion	LC-MS retention time
330		Intermediate 138	464	2.9
331		Intermediate 137	464	2.88
332		Intermediate 140	478	2.96
333		Intermediate 82b	478	3
334		Bionet Research	470	2.87
335		Lancaster	450	2.78
336		J. Pharm. Pharmacol; 1997, 49 (1), 10-15	484	2.98
337		US4154599 (1980)	468	2.84
338		Intermediate 75a	464	2.74
339		Intermediate 142	478	2.88
340		Intermediate 80a	492	2.99
341		Intermediate 83a	502	2.9

342		Intermediate 144	478	2.83
343		Intermediate 143	478	2.85
344		Intermediate 141	478	2.85
345		Intermediate 145	492	2.95

Examples 346 to 351

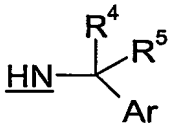
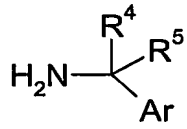
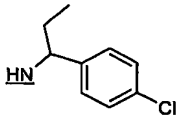
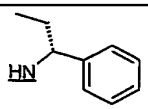


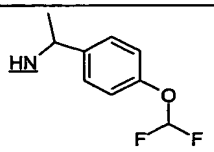
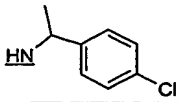
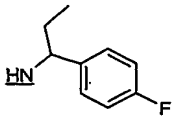
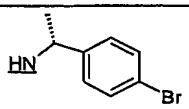
(of which, Example 348 is believed to be a mixture of isomers enriched in a major isomer believed to have the (R)-stereochemistry at the benzylic carbon atom)

General Procedure:

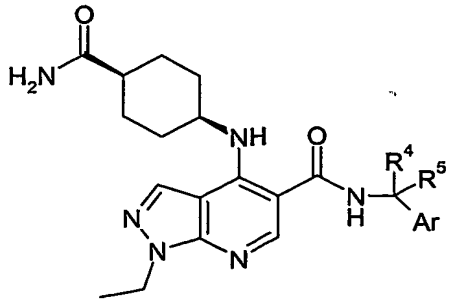
A mixture of Intermediate 120 (0.1mmol), HATU (0.1mmol) and DIPEA (0.4mmol) in DMF (0.4ml) was shaken at room temperature for 10 min. A solution of the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.1mmol) in DMF (0.2ml) was then added and the mixture was agitated for several minutes to give a solution. The solution was stored at room temperature for 16-64 hours then concentrated *in vacuo*. The residue was dissolved in chloroform (0.5ml) and applied to a SPE cartridge (aminopropyl, 0.5g). The cartridge was eluted successively with chloroform (1.5ml), EtOAc (1.5ml) and EtOAc:MeOH (9:1, 1.5ml). Fractions containing the desired product were concentrated *in vacuo* and the residue purified by mass directed autoprep HPLC.

The following Examples 346 to 351 were prepared from Intermediate 120 and the appropriate amine reagent Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure. The Examples were isolated as a mixture of *cis* and *trans* isomers (at the cyclohexane ring), with the *cis* isomer predominating.

Example Number	 (connecting nitrogen underlined)	**One Possible Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
346		J. Pharm. Pharmacol; 1997, 49 (1), 10-15	483	3.09
347		Lancaster	449	2.88

348		Intermediate 65	501	2.95
349		Bionet Research	469	2.98
350		US 4154599 (1980)	467	2.94
351		Lancaster	513	3.02

Examples 352 to 355

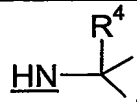
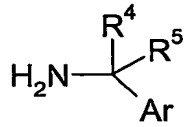
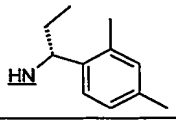
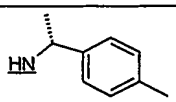
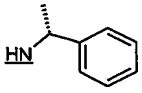
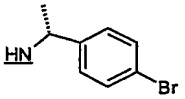


(of which, at least Example 352 is believed to consist essentially of isomer(s) believed to have the (R)-stereochemistry at the benzylic carbon atom, as shown below)

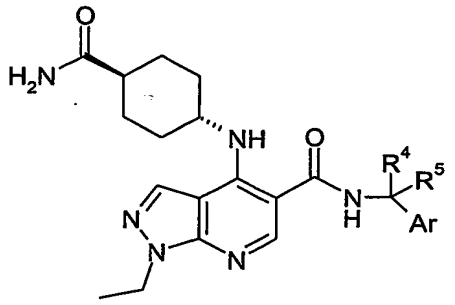
General Procedure:

A mixture of Intermediate 120 (0.09mmol), EDC (0.1mmol) and HOBT (0.1mmol) in DMF (1ml) was stirred at room temperature for 30 min. DIPEA (0.23mmol) was added and the solution was added to the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.12mmol) in DMF. The mixture was stirred for 30min. then left to stand at room temperature for 16 hours. The solvent was evaporated. The residue was partitioned between DCM and saturated sodium bicarbonate solution. The organic phase was separated and evaporated. The residue was purified by mass directed autoprep HPLC to obtain the desired product.

The following Examples 352 to 355 were prepared from Intermediate 120 and the appropriate amine reagent Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

Example Number	 (connecting nitrogen underlined)	**One Possible Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
352		Intermediate 82b	477	2.92
353		Lancaster	449	2.72
354		Aldrich	435	2.63
355		Lancaster	513	2.90

Examples 356 to 359

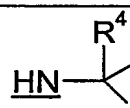
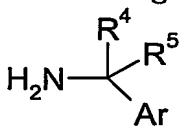
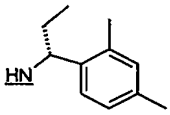
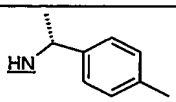
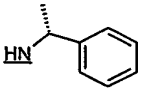
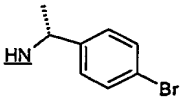


(of which, at least Example 356 is believed to consist essentially of isomer(s) believed to have the (R)-stereochemistry at the benzylic carbon atom, as shown below)

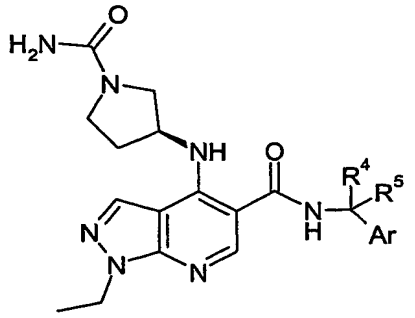
General Procedure:

A mixture of Intermediate 121 (0.09mmol), EDC (0.1mmol) and HOBT (0.1mmol) in DMF (1ml) was stirred at room temperature for 30 min. DIPEA (0.23mmol) was added and the solution was added to the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.12mmol) in DMF. The mixture was stirred for 30min. then left to stand at room temperature for 16 hours. The solvent was evaporated. The residue was partitioned between DCM and saturated sodium bicarbonate solution. The organic phase was separated and evaporated. The residue was purified by mass directed autoprep HPLC to obtain the desired product.

The following Examples 356 to 359 were prepared from Intermediate 121 and the appropriate amine reagent Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

Example Number	 (connecting nitrogen underlined)	One Possible Source of amine reagent 	MH^+ Ion	LC-MS retention time
356		Intermediate 82b	477	2.98
357		Lancaster	449	
358		Aldrich	435	2.65
359		Lancaster	513	2.90

Examples 360 to 363

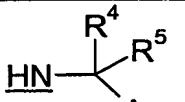
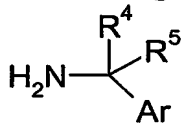
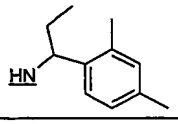
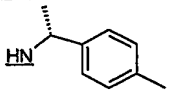
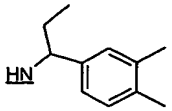
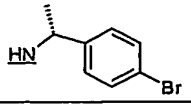


(of which, Examples 360 and possibly Example 362 are believed to be mixtures of diastereoisomers enriched in a major diastereoisomer believed to have the (R)-stereochemistry at the benzylic carbon atom)

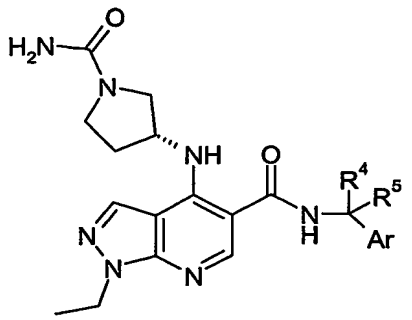
General Procedure:

A mixture of Intermediate 152 (30mg), HATU (120mg) and DIPEA (0.09ml) in acetonitrile (2ml) was added to the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.09mmol). The mixture was left to stand at room temperature for 16 hours. The solvent was evaporated. The residue was partitioned between DCM and saturated sodium bicarbonate solution. The organic phase was separated and evaporated. The residue was purified by mass directed autoprep HPLC to obtain the desired product.

The following Examples 360 to 363 were prepared from Intermediate 152 and the appropriate amine reagent Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

Example Number	 (connecting nitrogen underlined)	One Possible Source of amine reagent 	MH^+ Ion	LC-MS retention time
360		Intermediate 82	464	2.8
361		Lancaster	436	2.6
362		Intermediate 84	464	2.8
363		Lancaster	500+ 502	2.7

Examples 364 to 367

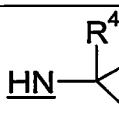
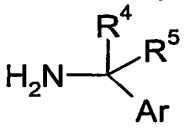
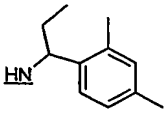
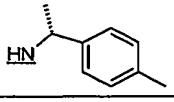
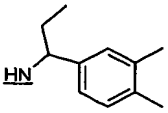
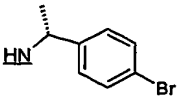


(of which, Examples 364 and possibly 366 are believed to be mixtures of diastereoisomers enriched in a major diastereoisomer believed to have the (R)-stereochemistry at the benzylic carbon atom)

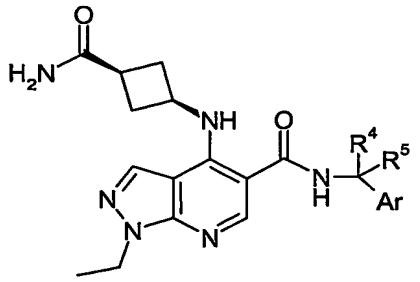
General Procedure:

A mixture of Intermediate 153 (30mg), HATU (120mg) and DIPEA (0.09ml) in acetonitrile (2ml) was added to the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.09mmol). The mixture was left to stand at room temperature for 16 hours. The solvent was evaporated. The residue was partitioned between DCM and saturated sodium bicarbonate solution. The organic phase was separated and evaporated. The residue was purified by mass directed autoprep HPLC to obtain the desired product.

The following Examples 364 to 367 were prepared from Intermediate 153 and the appropriate amine reagent Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

Example Number	 (connecting nitrogen underlined)	**One Possible Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
364		Intermediate 82	464	2.81
365		Lancaster	436	2.62
366		Intermediate 84	464	2.82
367		Lancaster	500 + 502	2.74

Examples 368 to 369

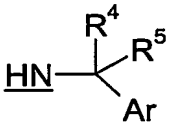
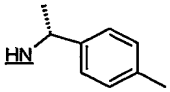
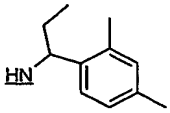


Example 368

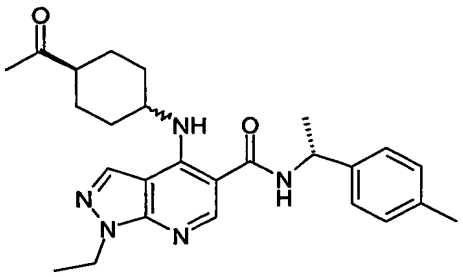
A mixture of Intermediate 108 (25mg), *cis*-3-aminocyclobutanecarboxamide (Chemical Abstracts Service, CAS 84182-57-0) (10mg) and DIPEA (23mg) in acetonitrile (4ml) was heated at reflux for 24h. The reaction mixture was cooled and the solvent was evaporated. The residue was purified by mass directed autoprep HPLC to give Example 368 (19mg) as a white solid.

Example 369

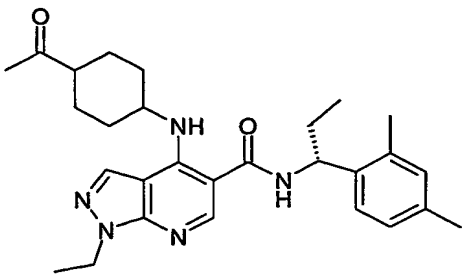
Example 369 was prepared from *cis*-3-aminocyclobutanecarboxamide and Intermediate 122 using a procedure similar to that used for the preparation of Example 368.
Example 369 is believed to be a mixture of isomers enriched in a major isomer believed to have the (R)-stereochemistry at the benzylic carbon atom.

Example Number	 (connecting nitrogen underlined)	Source of aryl chloride	MH^+ Ion	LC-MS retention time
368		Intermediate 108	421	2.78
369		Intermediate 122	449	3.01

Examples 370 to 372



Example 370: trans- at cyclohexane ring
Example 372: cis- at cyclohexane ring



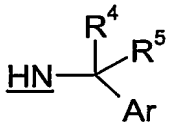
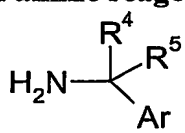
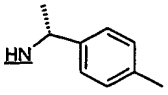
Example 371

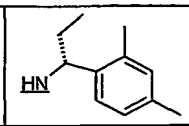
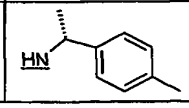
(of which, Example 371 is a mixture of isomers enriched in a major isomer(s) believed to have the (R)-stereochemistry at the benzylic carbon atom)

A mixture of Intermediate 158 (23mg), EDC (15mg), HOBT (10.5mg) and DIPEA (27ul) in DMF (1ml) was stirred at room temperature for 30 min. then added to [(1*R*)-1-(4-methylphenyl)ethyl]amine (10.5mg) (e.g. available from Lancaster). The mixture was stirred for 3h. and then left to stand at room temperature for 16 hours. More EDC (7.5mg) and HOBT (5.3mg) were added and the mixture was left to stand for 3h. More [(1*R*)-1-(4-methylphenyl)ethyl]amine (5.3mg) was added and the mixture was left to stand overnight. The solvent was evaporated. The residue was partitioned between DCM and saturated sodium bicarbonate. The organic phase was separated and evaporated. The residue was purified by mass directed autoprep HPLC to obtain **Example 370** (10.1mg; major component, contains 4-(*trans*-4-acetylcyclohexyl)amino group).

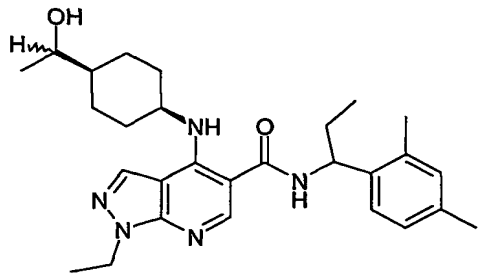
The isomeric ketone, **Example 372**, was isolated as a minor component (3.7mg, contains 4-(*cis*-4-acetylcyclohexyl)amino group) from the purification of Example 370.

The following **Example 371** (mixture of *cis* and *trans* isomers at cyclohexane ring, and believed to consist essentially of isomers believed to have the (R)-stereochemistry at the benzylic carbon atom) was prepared from Intermediate 158 and the appropriate amine reagent (preferably Intermediate 82b) using the above procedure or a similar procedure:

Example Number	 (connecting nitrogen underlined)	**One Possible Source of amine reagent** 	**MH^+ Ion**	**LC-MS retention time**
370		Lancaster	448	3.17

371		Intermediate 82b	476	3.39, 3.41
372		Lancaster	448	3.14

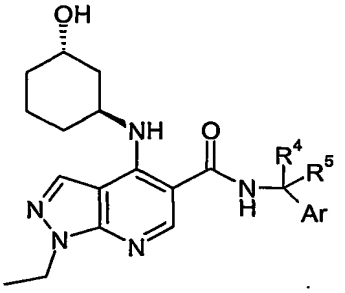
Example 373: 4-{[*cis*-4-(1-hydroxyethyl)cyclohexyl]amino}-N-[1-(2,4-dimethylphenyl)propyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



(believed to be a mixture of isomers enriched in a major isomer(s) believed to have the (R)-stereochemistry at the benzylic carbon atom)

A mixture of Intermediate 122 (13mg), Intermediate 160 (7mg) and DIPEA (0.3ml) in ethanol (1ml) was stirred and heated at reflux overnight. The mixture was cooled and the solvent was evaporated. The residue was partitioned between DCM and sodium bicarbonate solution. The organic phase was concentrated. The residue was passed through a silica column, using a mixture of cyclohexane and EtOAc as the eluent, to give Example 373 (3mg). LCMS showed $MH^+ = 478$; $T_{RET} = 3.35$min.

Examples 374 to 378



relative stereochemistry at cyclohexane ring as drawn, racemic;
i.e. *trans*-(3-hydroxycyclohex-1-yl)amino, racemic
= (*trans*-3-hydroxycyclohexyl)amino group, racemic

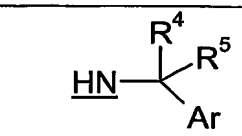
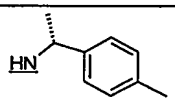
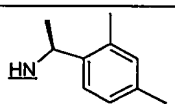
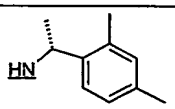
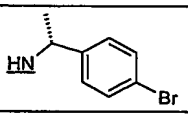
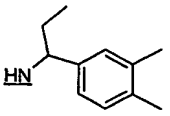
(of which Example 378 is believed to be a mixture of isomers enriched in a major isomer(s) believed to have the (R)-stereochemistry at the benzylic carbon atom;

and of which Examples 375 and 376 are believed to consist essentially of isomer(s) believed to have the stereochemistry at the benzylic carbon atom shown below)

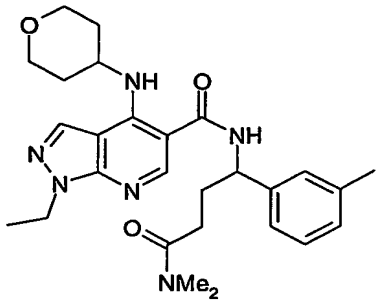
General Procedure:

A mixture of Intermediate 162 (25mg), HATU (32mg) and DIPEA (68ul) in acetonitrile (2ml) was added to the amine reagent Ar-C(R^4)(R^5)-NH_2 (0.08mmol). The mixture was left to stand at room temperature for 72 hours. The solvent was evaporated. The residue was purified by mass directed autoprep HPLC to obtain the desired product.

The following Examples 374-378 were prepared from Intermediate 162 and the appropriate amine reagent Ar-C(R^4)(R^5)-NH_2 using this or a similar procedure:

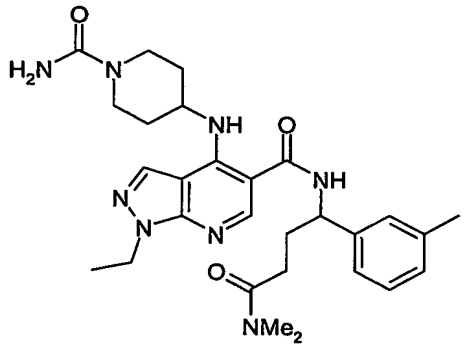
Example Number	 (connecting nitrogen underlined)	**One Possible Source of amine reagent** Ar-C(R^4)(R^5)-NH_2	**MH^+ Ion**	**LC-MS retention time**
374		Lancaster	422	3.10
375		Intermediate 101	436	3.23
376		Intermediate 100	436	3.24
377		Lancaster	487	3.24
378		Intermediate 84	450	3.32

Example 379: N-[4-(dimethylamino)-1-(3-methylphenyl)-4-oxobutyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



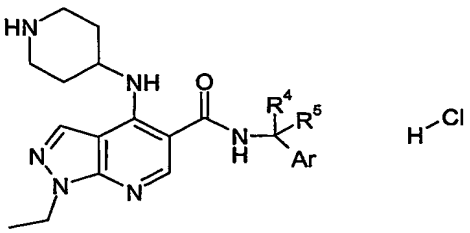
A mixture of Intermediate 13 (19mg), HOBT (10mg), EDC (14mg) and DIPEA (26mg) in acetonitrile (2.5ml) was stirred for 10min then added to Intermediate 169 (20mg). The solution was stirred for 3h then left to stand overnight at room temperature. More DIPEA (53mg) was added. The reaction mixture was stirred for 6h then left to stand for 3 days at room temperature. The solvent was removed *in vacuo*. The residue was partitioned between DCM and 1M sodium bicarbonate solution. The organic phase was separated, washed with water and concentrated *in vacuo*. The residue was purified by passing through a 1g SPE cartridge, using ethyl acetate containing 50-0% cyclohexane as the eluent, to give Example 379 (18mg) as a colourless gum. LCMS showed $MH^+ = 493$; $T_{RET} = 2.83$min.

Example 380: 4-{[1-(aminocarbonyl)-4-piperidinyl]amino}-N-[4-(dimethylamino)-1-(3-methylphenyl)-4-oxobutyl]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



Example 380 was prepared from Intermediate 105 and Intermediate 169 using a procedure similar to that used to prepare Example 379. LCMS showed $MH^+ = 535$; $T_{RET} = 2.61$min.

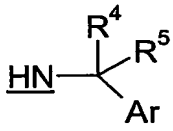
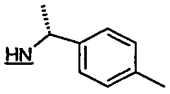
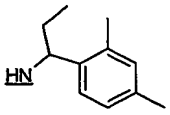
Examples 381 to 382



General Procedure:

A solution of the appropriate intermediate carbamate (Intermediate 164 or 165; 0.2 to 0.25mmol) in a 4M solution of hydrogen chloride in dioxan (5ml) was stirred for 1h at room temperature. The solution was concentrated *in vacuo* to leave the product as a solid.

The following Examples 381 and 382 were prepared in this manner:

Example Number	 (connecting nitrogen underlined)	**Starting material**	**MH^+ Ion**	**LC-MS retention time**
381 (as hydrochloride)		Intermediate 164	407	2.34
382 (as hydrochloride)		Intermediate 165	435	2.51

Example 382 is believed to be a mixture of isomers with the major isomer believed to have the (R)-stereochemistry at the benzylic carbon atom.